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NEWS	6	MAR 03	MEDLINE and LMEDLINE reloaded
NEWS	7	MAR 03	MEDLINE file segment of TOXCENTER reloaded
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FILE 'MEDLINE' ENTERED AT 17:25:06 ON 13 APR 2004

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FILE 'CAPLUS' ENTERED AT 17:25:06 ON 13 APR 2004

=> s treatment
L1 7779567 TREATMENT

=> s l1 and allergy
L2 39386 L1 AND ALLERGY

=> s l2 and cholera toxin B subunit
L3 10 L2 AND CHOLERA TOXIN B SUBUNIT

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PROCESSING COMPLETED FOR L3
L4 6 DUP REMOVE L3 (4 DUPLICATES REMOVED)

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L4 ANSWER 1 OF 6 EMBASE
on STN
2003192785 EMBASE Mucosal adjuvants and anti-infection and anti-immunopathology vaccines based on cholera toxin, **cholera toxin B subunit** and CpG DNA. Holmgren J.;
Harandi A.M.; Czerkinsky C.. J. Holmgren, Department of Medical Microbiology, Goteborg Univ. Vacc. Res. Institute, Goteborg University, Guldhedsgatan 10A, SE-413 46 Goteborg, Sweden.
jan.holmgren@microbio.gu.se. Expert Review of Vaccines 2/2 (205-217) 2003.
Refs: 64.
ISSN: 1476-0584. CODEN: ERVXAX. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB The mucosal immune system consists of an integrated network of lymphoid cells that work in concert with innate host factors to promote host defence. Mucosal immunization can be used both to protect the mucosal surfaces against colonization and invasion by microbial pathogens and to provide a means for immunological **treatment** of selected autoimmune, allergic or infectious-immunopathological disorders through the induction of antigen-specific tolerance. The development of mucosal vaccines, whether for prevention of infectious diseases or for oral tolerance immunotherapy, requires efficient antigen delivery and adjuvant systems. Significant progress has recently been made to generate partly or wholly detoxified derivatives of cholera toxin (including the completely nontoxic **cholera toxin B subunit**)
and the closely related Escherichia coli heat-labile enterotoxin, with retained adjuvant activity. **Cholera toxin B subunit** is a protective component of a widely registered oral vaccine against cholera, and has proven to be a promising vector for either giving rise to anti-infective immunity or for inducing peripheral anti-inflammatory tolerance to chemically or genetically linked foreign antigens administered mucosally. Promising advances have also recently been made In the design of efficient mucosal adjuvants based on bacterial

DNA that contains CpG-motifs and various imidazoquinoline compounds binding to different Toll-like receptors on mucosal antigen-presenting cells.

L4 ANSWER 2 OF 6 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2002069171 EMBASE Induction of mucosal tolerance to Bet v 1, the major birch pollen allergen - A review. Wiedermann U.; Kraft D.. Prof. U. Wiedermann, Department of Pathophysiology, University Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. ursula.wiedermann@akh-wien.ac.at. Allergy and Clinical Immunology International 14/1 (17-24) 2002.
Refs: 99.
ISSN: 0838-1925. CODEN: ACIIFH. Pub. Country: Switzerland. Language: English. Summary Language: English.

AB Background: The major birch pollen allergen Bet v 1 is one of the most prevalent environmental allergens responsible for allergic airway inflammation in man. Mucosal application of soluble antigens leads to a state of antigen-specific, systemic nonresponsiveness, termed oral/mucosal tolerance. Within recent years there has been increasing interest in mucosal tolerance induction to be used as a **treatment** strategy against immunological disorders, including type I **allergies**. Methods/data base: A mouse model of allergic asthma was used to study the effectiveness of mucosal tolerance induction with recombinant Bet v 1 and hypoallergenic molecules thereof. In addition certain mucosal adjuvants/mucosal antigen delivery systems in conjunction with the allergen were used to prevent or treat type I allergic immune responses to birch pollen and its major allergen Bet v 1. Results: Inhalation of birch pollen antigen in conjunction with the mucosal adjuvant cholera-toxin induced a Th1-like response in naive animals and modulated an already established allergic immune response. Intranasal application of Bet v 1 conjugated to the nontoxic cholera toxin B (CTB)-subunit enhanced subsequent allergic sensitization, whereas CTB coupled to the dietary allergen ovalbumin reduced antigen-specific immunoglobulin E (IgE) production, indicating that the effects of the mucosal antigen delivery system depended on the nature of the coupled allergen. Mucosal (nasal and oral) administration of unconjugated Bet v 1 or hypoallergenic derivatives thereof could inhibit/suppress allergic sensitization and airway inflammation in naive and in sensitized animals. Conclusion: We conclude from our studies that mucosal tolerance induction with recombinant allergens and their hypoallergenic derivatives - with or without the use of mucosal adjuvants - could provide a safe and convenient alternative **treatment** to conventional immunotherapy.

L4 ANSWER 3 OF 6 MEDLINE on STN DUPLICATE 1

2000385105. PubMed ID: 10848926. Prolonged oral **treatment** with low doses of allergen conjugated to **cholera toxin B subunit** suppresses immunoglobulin E antibody responses in sensitized mice. Rask C; Holmgren J; Fredriksson M; Lindblad M; Nordstrom I; Sun J B; Czerkinsky C. (Department of Medical Microbiology and Immunology, Goteborg University, Goteborg, Sweden.) Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology, (2000 Jul) 30 (7) 1024-32. Journal code: 8906443. ISSN: 0954-7894. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: Oral tolerance is a long recognized method for inducing systemic immunological tolerance. However, large doses of antigen and frequent administrations are often required. By linking the antigen to the nontoxic mucosa-binding B subunit of cholera toxin (CTB), the required amount can be dramatically reduced. We have previously shown that mucosal administration of small amounts of antigens coupled to CTB can suppress peripheral Th1 cell-reactivity and associated inflammatory immunopathology in both naive and systemically-immunized animals. Induction of oral tolerance by repeated feeding of relatively small doses of antigen has, in some cases been shown to involve the generation of regulatory Th2-like

CD4+ T cells, and hence could promote rather than suppress type I immunoglobulin (Ig) E-mediated allergic responses. OBJECTIVES: We examined whether oral prophylactic or therapeutic administration of a model allergen coupled to CTB would modulate allergen-specific IgE responses in high IgE responder Balb/c mice. METHODS: Ovalbumin (OVA) was used as a model allergen. Mice were treated perorally with free or CTB-coupled OVA before or after systemic priming with alum-adsorbed OVA. Allergen-specific IgE levels in serum were measured with the passive cutaneous anaphylaxis test at various time-points. RESULTS: Oral administration of a single low dose of CTB-linked OVA, prior to systemic sensitization and challenge with OVA, suppressed allergen-specific serum IgE antibody responses. **Treatment** with comparable doses of free OVA was much less effective. Most importantly, oral **treatment** with CTB-OVA conjugate could also suppress an already initiated IgE antibody response, but to achieve such a 'therapeutic effect', administration of multiple low doses of conjugate over a long time was required. Oral **treatment** with CTB-OVA conjugate could also effectively suppress antigen-specific Th1-mediated delayed-type hypersensitivity. Thus **treatment** with a CTB-conjugated model allergen can affect a broad range of T-cell-driven immune responses, even in antigen-experienced animals. CONCLUSION: These results may impact on the development of therapeutic vaccines against type I **allergies**
.

L4 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
2000:885735 Document No. 135:18506 Enhanced immunological tolerance against allograft rejection by oral administration of allogeneic antigen linked to **cholera toxin B subunit**. Sun, Jia-Bin; Li, Bin-Ling; Czerkinsky, Cecil; Holmgren, Jan (Department of Medical Microbiology and Immunology, Goteborg University, Goteborg, S-413 46, Swed.). Clinical Immunology (Orlando, Florida), 97(2), 130-139 (English) 2000. CODEN: CLIIFY. ISSN: 1521-6616. Publisher: Academic Press.

AB A single oral intragastric administration of **cholera toxin B subunit** (CTB) conjugated to allogeneic thymocytes (ATC, 4 + 107 cells) under conditions allowing the CTB to bind the complex to GM1 ganglioside receptors was shown to be efficacious in inducing peripheral T cell tolerance associated with significant suppression of both primary and secondary accelerated rejection of heart allografts when tested in mice. Allogeneic in vivo delayed-type hypersensitivity (DTH), in vitro cytotoxicity responses, and mixed lymphocyte reactions (MLR) by T cells from mesenteric lymph nodes (MLN), popliteal lymph nodes (PLN), and spleen were significantly reduced in mice treated with the CTB-ATC conjugate, as were also the nos. of cells in these organs producing IL-2, IFN-γ, or IL-4. In contrast, a marked increase in the production of IL-4 in Peyer's patches (PP) and of TGF-β1 in PLN was observed The suppressive potential of T cells from PP and/or MLN after oral **treatment** with CTB-ATC was further evident by i.p. transfer of such cells from CTB-ATC-treated animals to primed recipients, which led to marked suppression of both allogen-specific DTH and MLR responses. A critical role for PP in inducing peripheral tolerance after oral CTB-ATC **treatment** was indicated by the absence of tolerance induction in animals whose PP had been destroyed before **treatment** with CTB-ATC. The results indicate that the protection against allograft rejection by oral **treatment** with CTB-ATC is mediated by T cells and associated with a strong induction of IL-4 production at mucosal sites and TGF-β1 at the effector sites. (c) 2000 Academic Press.

L4 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
1999:52433 Document No. 130:250778 Oral tolerance and anti-pathological vaccines. Czerkinsky, C.; Sun, J.-B.; Holmgren, J. (INSERM Unit 364, Cellular and Molecular Immunology, Faculte de Medecine-Pasteur, Nice, 06107, Fr.). Current Topics in Microbiology and Immunology, 236(Defense

of Mucosal Surfaces: Pathogenesis, Immunity and Vaccines), 79-91 (English) 1999. CODEN: CTMIA3. ISSN: 0070-217X. Publisher: Springer-Verlag.
AB A review with 50 refs. Topics discussed include mechanism of induction and expression of peripheral tolerance after mucosal delivery of antigens; mucosal immunotherapy; **cholera toxin B subunit** as a mucosal carrier-immunomodulating system for anti-pathol. vaccination; **treatment** of organ-specific autoimmune diseases; prevention of graft rejection and type I **allergies**; and mucosal vaccines for simultaneous induction of anti-infectious and anti-pathol. immunity.

L4 ANSWER 6 OF 6 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
97326083 EMBASE Document No.: 1997326083. Oral administration of antigen in the **treatment** of eye disease. Williams K.A.. K.A. Williams, Department of Ophthalmology, Flinders University South Australia, Adelaide, SA, Australia. British Journal of Ophthalmology 81/9 (714-715) 1997.
Refs: 19.
ISSN: 0007-1161. CODEN: BJOPAL. Pub. Country: United Kingdom. Language: English.

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=> s l2 and mucosal adjudvant
L5            0 L2 AND MUCOSAL ADJUDVANT

=> s l2 and E coli enterotoxin B subunit
L6            0 L2 AND E COLI ENTEROTOXIN B SUBUNIT

=> s l2 and "Etx"
L7            0 L2 AND "ETX"

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     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 17:25:06 ON
     13 APR 2004
L1       7779567 S TREATMENT
L2         39386 S L1 AND ALLERGY
L3            10 S L2 AND CHOLERA TOXIN B SUBUNIT
L4             6 DUP REMOVE L3 (4 DUPLICATES REMOVED)
L5             0 S L2 AND MUCOSAL ADJUDVANT
L6             0 S L2 AND E COLI ENTEROTOXIN B SUBUNIT
L7             0 S L2 AND "ETX"

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L8            0 L2 AND "ETXB"

=> s l2 and E coli heat label enterotoxin
L9            0 L2 AND E COLI HEAT LABEL ENTEROTOXIN

=> s l2 and enterotoxin
L10          32 L2 AND ENTEROTOXIN

=> dup remove l10
PROCESSING COMPLETED FOR L10
L11           30 DUP REMOVE L10 (2 DUPLICATES REMOVED)

=> d l11 1-30 cbib abs

L11 ANSWER 1 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
2003:991374 Document No. 140:40879 Bifunctional CpG or oligo-/polynucleotide
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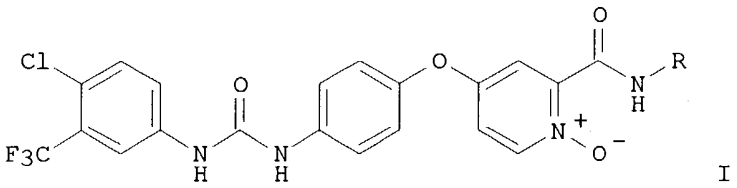
and toxin or **enterotoxin** containing composition. Holmgren, Jan; Harandi, Ali M. (Gotovax AB, Swed.). PCT Int. Appl. WO 2003103708 A1 20031218, 46 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-SE935 20030605. PRIORITY: SE 2002-1701 20020605; US 2002-PV385588 20020605.

AB A bifunctional composition comprising an intracellularly effective immunomodulating nucleic acid component containing at least one immunostimulatory, immunoinhibitory, or immunomodulating motif and selected from a mononucleotide, a dinucleotide, an oligonucleotide or a polynucleotide with either a natural phosphodiester backbone or a modified backbone, optionally in combination with a specific antigen, in association with a protein binding to specific receptors on mammalian cell surfaces selected from the group consisting of cholera toxin (CT), the subunit B of CT (CTB), Escherichia coli heat-labile **enterotoxin** (LT), the subunit B of LT (LTB), and proteins or protein derivs. that react with antiserum to CT or LT, bind to GM1 ganglioside, ADP-ribosylates an acceptor protein, or give rise to accumulation of cAMP in target cells, and antibodies or other proteins which after binding to a specific cell surface component can be internalized into the cell, is described. The composition is useful for **treatment** of tumors, infections, graft rejections, immunosuppressive states, autoimmune diseases and **allergies**, and further with a specific antigen it is useful for immunoprophylaxis, immunotherapy or induction of tolerance, and for **treatment** ex vivo of an antigen-presenting cell for subsequent infusion into a mammal for vaccination or immunotherapy purposes.

L11 ANSWER 2 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN

2003:656581 Document No. 139:197370 Preparation of aryl ureas containing pyridine, quinoline and isoquinoline N-oxide functionality as kinase inhibitors. Dumas, Jacques; Scott, William J.; Riedl, Bernd (Bayer Corporation, USA). PCT Int. Appl. WO 2003068229 A1 20030821, 67 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US4110 20030211. PRIORITY: US 2002-PV354935 20020211.

GI



I

AB The title ureas containing a pyridine, quinoline, or isoquinoline functionality which is oxidized at the nitrogen heteroatom MLBNHCONHA [A =

(un)substituted Ph, naphthyl, 5-6 membered monocyclic heteroaryl, 8-10 membered bicyclic heteroaryl; B = (un)substituted phenylene, naphthylene, 5-6 membered monocyclic heteroarylene, 8-10 membered bicyclic heteroarylene; L = (CH2)mO(CH2)l, (CH2)m(CH2)l, (CH2)mCO(CH2)l, etc.; m, l = 0-4; M = (un)substituted pyridine-1-oxide, quinoline-1-oxide, isoquinoline-1-oxide; with the provisos] which are useful in the **treatment** of (i) raf mediated diseases, for example, cancer, (ii) p38 mediated diseases such as inflammation and osteoporosis, and (iii) VEGF mediated diseases such as angiogenesis disorders, were claimed. Preparation of two ureas such as I [R = H, Me] which are not compds. of the invention, and have been distinguished from the compds. of the invention by a proviso, was described. Pharmaceutical composition comprising the title ureas was claimed.

L11 ANSWER 3 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
2003:656580 Document No. 139:197369 Preparation of aryl ureas with angiogenesis inhibiting activity. Dumas, Jacques; Scott, William J.; Elting, James; Hatoum-Makdad, Holia (Bayer Corporation, USA). PCT Int. Appl. WO 2003068228 A1 20030821, 83 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US4103 20030211. PRIORITY: US 2002-PV354950 20020211.

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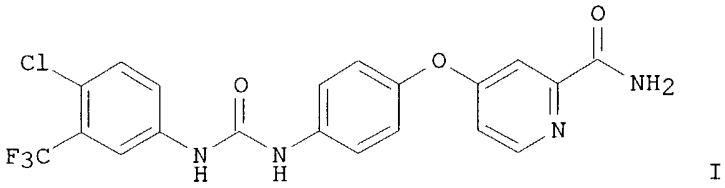

I

AB The title compds. ANHCONHB [A, B = (un)substituted Ph, naphthyl, 5-6 membered monocyclic heteroaryl, etc.], useful for treating diseases mediated by the VEGF induced signal transduction pathway characterized by abnormal angiogenesis or hyperpermeability processes, were claimed. Prepns. of three title ureas are described. E.g., a 3-step synthesis of the urea I (starting from Me 4-chloro-2-pyridinecarboxylate hydrochloride), was given. The KDR (VEGFR2) assay for testing the title ureas is described.

L11 ANSWER 4 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
2003:633041 Document No. 139:178680 Compound and method for the prevention and/or the **treatment** of **allergy**. Saint-Remy, Jean-Marie; Jacquemin, Marc (Belg.). U.S. Pat. Appl. Publ. US 2003152581 A1 20030814, 26 pp., Cont.-in-part of U.S. 6,602,509. (English). CODEN: USXXCO. APPLICATION: US 2002-237656 20020910. PRIORITY: EP 1998-870167 19980730; US 1999-362731 19990729.

AB The present invention is related to a compound for the prevention and/or the **treatment** of **allergy** consisting of: at least one allergen antigenic determinant which is recognized by a B cell or an antibody secreted by a B cell of a non-atopic individual to said allergen, and at least one antigenic determinant of an antigen different from said allergen which triggers T cell activation.

L11 ANSWER 5 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2003192785 EMBASE Mucosal adjuvants and anti-infection and anti-immunopathology vaccines based on cholera toxin, cholera toxin B subunit and CpG DNA. Holmgren J.; Harandi A.M.; Czerkinsky C.. J. Holmgren, Department of Medical Microbiology, Goteborg Univ. Vacc. Res. Institute, Goteborg University, Guldhedsgatan 10A, SE-413 46 Goteborg, Sweden. jan.holmgren@microbio.gu.se. Expert Review of Vaccines 2/2 (205-217) 2003.
Refs: 64.
ISSN: 1476-0584. CODEN: ERVXAX. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB The mucosal immune system consists of an integrated network of lymphoid cells that work in concert with innate host factors to promote host defence. Mucosal immunization can be used both to protect the mucosal surfaces against colonization and invasion by microbial pathogens and to provide a means for immunological **treatment** of selected autoimmune, allergic or infectious-immunopathological disorders through the induction of antigen-specific tolerance. The development of mucosal vaccines, whether for prevention of infectious diseases or for oral tolerance immunotherapy, requires efficient antigen delivery and adjuvant systems. Significant progress has recently been made to generate partly or wholly detoxified derivatives of cholera toxin (including the completely nontoxic cholera toxin B subunit) and the closely related Escherichia coli heat-labile **enterotoxin**, with retained adjuvant activity.
Cholera toxin B subunit is a protective component of a widely registered oral vaccine against cholera, and has proven to be a promising vector for either giving rise to anti-infective immunity or for inducing peripheral anti-inflammatory tolerance to chemically or genetically linked foreign antigens administered mucosally. Promising advances have also recently been made In the design of efficient mucosal adjuvants based on bacterial DNA that contains CpG-motifs and various imidazoquinoline compounds binding to different Toll-like receptors on mucosal antigen-presenting cells.

L11 ANSWER 6 OF 30 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2003:338239 Document No.: PREV200300338239. Variation of gene expression in PBMC after stimulation with staphylococcal **enterotoxin** B (SEB) among dexamethasone and FK506. Akasawa, A. [Reprint Author]. National Research Institute for Child Health and Development, Tokyo, Japan. Journal of Allergy and Clinical Immunology, (February 2003) Vol. 111, No. 2 Abstract Supplement, pp. S130. print.
Meeting Info.: AAAAI 60th Anniversary Meeting. Denver, CO, USA. March 07-12, 2003. American Academy of Allergy, Asthma and Immunology.
CODEN: JACIBY. ISSN: 0091-6749. Language: English.

L11 ANSWER 7 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
2002:142872 Document No. 136:211910 Human claudin 19, claudin 21 and claudin 22 which are associated with tight junctions, protein sequence and uses in therapy. Youakim, Adel; Dubose, Robert F.; Wiley, Steven R. (Immunex Corporation, USA). PCT Int. Appl. WO 2002014499 A2 20020221, 65 pp.
DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US25662 20010815. PRIORITY: US 2000-PV225794 20000815; US 2000-PV225513 20000815.
AB The invention relates to new members of claudin polypeptide family, human

claudin 19, claudin 21 and claudin 22. The invention provides an expression vector, host cells and methods for recombinant production of said claudins. The invention also relates to use of said said claudins in a methods for treating disorders related to tight junction formation and epithelial or endothelial barrier functions. The invention also relates to identification of agents that modulate said claudins polypeptide activities.

L11 ANSWER 8 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN

2002:409267 Document No. 137:6098 Heteroaryl ureas containing nitrogen hetero-atoms as p38 kinase inhibitors. Dumas, Jacques; Riedl, Bernd; Khire, Uday; Sibley, Robert N.; Hatoum-Mokdad, Holia; Monahan, Mary-katherine; Gunn, David E.; Lowinger, Timotthy B.; Scott, William J.; Smith, Roger A.; Wood, Jill E. (Bayer Corporation, USA). U.S. Pat. Appl. Publ. US 2002065296 A1 20020530, 39 pp., Cont.-in-part of U. S. Ser. No. 778,039. (English). CODEN: USXXCO. APPLICATION: US 2001-838286 20010420. PRIORITY: US 1999-PV115878 19990113; US 1999-257265 19990225; US 1999-425229 19991022; US 2001-778039 20010207.

AB This invention relates to the use of a group of heteroaryl ureas (I; for example, N-(2-methoxy-3-quinolyl)-N'-[4-[3-(N-methylcarbamoyl)phenoxy]phenyl]urea) containing N in treating p38 mediated diseases, and pharmaceutical compns. for use in such therapy. I is A-NHC(O)NH-B or a pharmaceutically acceptable salt thereof, wherein A is a substituted or unsubstituted pyridyl, quinolinyl or isoquinolinyl group, B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 50 C atoms with a cyclic structure bound directly to N, containing at least 5 cyclic members with 0-4 members of groups consisting of N, O and S. Information about the substituents for A and B are given in the claims. Although the methods of preparation are not claimed, 37 example prepns. are included as well as examples of preparation of intermediates. No pharmacol. data is included.

L11 ANSWER 9 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN

2002:878530 Document No. 138:71807 Hypersensitivity reactions after respiratory sensitization: effect of intranasal peptides containing T-cell epitopes. Jarnicki, Andrew G.; Tsuji, Takao; Thomas, Wayne R. (Centre for Child Health Research, TVW Telethon Institute for Child Health Research, University of Western Australia, West Perth, Australia). Journal of Allergy and Clinical Immunology, 110(4), 610-616 (English) 2002. CODEN: JACIBY. ISSN: 0091-6749. Publisher: Mosby, Inc..

AB Background: The intranasal administration of peptides containing T-cell epitopes has been shown to inhibit T-cell and antibody responses of mice injected with allergen, but responses to respiratory sensitization might be regulated differently. Objective: This study was designed to examine the effect of intranasal peptide on antigen-induced lung inflammatory responses and delayed hypersensitivity after sensitization by the respiratory mucosa or without sensitization. Methods: Mice were treated with an intranasal tolerizing regimen of a peptide containing the major T-cell epitope of Der p 1. Delayed hypersensitivity and lung inflammation to challenge with Der p 1 was measured either without further **treatment** or after sensitization induced by means of the intranasal administration of Der p 1 with a mutated **enterotoxin** adjuvant. Lung inflammatory responses were examined by means of lavage and histol. section, and delayed hypersensitivity responses were measured on the basis of ear swelling. Results: Delayed hypersensitivity reactions were induced in mice treated with intranasal peptide, and large reactions were found in mice given intranasal peptide and sensitized with intranasal Der p 1 and adjuvant. Mice pretreated with peptide and sensitized with Der p 1 had an increased lymphocytic infiltration after allergen-specific challenge, as measured by means of bronchoalveolar lavage and shown histol. These hypersensitivity results are in contrast to previous data that show tolerance to injected antigen. Conclusions: Although the intranasal administration of a peptide containing a T-cell epitope markedly

inhibits responses to sensitization produced by the injection of allergen, the peptide induces immune responses and increases hypersensitivity to respiratory sensitization.

L11 ANSWER 10 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2003064440 EMBASE Evaluation and prevalidation of an immunotoxicity test based on human whole-blood cytokine release. Langezaal I.; Hoffmann S.; Hartung T.; Coecke S.. S. Coecke, Eur. Ctr. Validation of Alt. Methods, Inst. for Health/Consumer Protection, Eur. Commn. Joint Research Centre, 21020 Ispra (VA), Italy. ATLA Alternatives to Laboratory Animals 30/6 (581-595) 2002.
Refs: 61.
ISSN: 0261-1929. CODEN: AALADQ. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Immunotoxicology is a relatively new field in toxicology, and is one of emerging importance, because immunotoxicity appears to contribute to the development of cancer, autoimmune disorders, **allergies** and other diseases. At present, there is a lack of human cell-based immunotoxicity assays for predicting the toxicity of xenobiotics toward the immune system in a simple, fast, economical and reliable way. Existing immunotoxicity tests are mainly performed in animals, although species differences favour humanbased testing. Whole-blood cytokine release models have attracted increasing interest, and are broadly used for pharmacological in vitro and ex vivo studies, as well as for pyrogenicity testing. We have adapted those methods for immunotoxicity testing, to permit the potency testing of immunostimulants and immunosuppressants. Following stimulation with a lipopolysaccharide or staphylococcal **enterotoxin** B, monocytes and lymphocytes release interleukin-1β and interleukin-4, respectively. Thirty-one pharmaceutical compounds, with known effects on the immune system, were used to optimise and standardise the method, by analysing their effects on cytokine release. The in vitro results were expressed as IC50 values for immunosuppression, and SC(4) (fourfold increase) values for immunostimulation, and compared with therapeutic serum concentrations of the compounds in patients, and in vivo LD50 values from animal studies. The in vitro results correlated well with the in vivo data, so the test appears to reflect immunomodulation. Results were reproducible (CV = 20 ± 5%), and the method could be transferred to another laboratory (r(2) = 0.99). We therefore propose this method for further validation and for use in immunotoxicity testing strategies.

L11 ANSWER 11 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2002421748 EMBASE Flare-up reaction on murine contact hypersensitivity: III. Effect of staphylococcal **enterotoxin** B. Natsuaki M.; Abe K.; Kitano Y.. M. Natsuaki, Department of Dermatology, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan. Journal of Dermatological Science 30/3 (233-239) 2002.
Refs: 32.
ISSN: 0923-1811. CODEN: JDSCEI.
Publisher Ident.: S 0923-1811(02)00110-X. Pub. Country: Ireland. Language: English. Summary Language: English.

AB Staphylococcal **enterotoxin** B (SEB), a bacterial superantigen, is known as an immunomodulator because it activates an extremely large number of T-cells, and induces the production of large amounts of cytokines. In this study, we examined the effects of SEB on the contact hypersensitivity reaction (CHR). BALB/c mice were first sensitized through haptens applied to the back, and CHR was then induced through challenge to the left ear using the same haptens. SEB was administered intravenously 4 weeks later, causing a flare-up, peaking at 24 h post-administration, in the left ear that had previously exhibited CHR. This flare-up reaction was hapten non-specific, and was inhibited by anti-mouse tumor necrosis factor (TNF)-α antibodies. The flare-up was also suppressed by the oral

administration of cyclosporin A prior to the administration of SEB. These results suggest that SEB induces a flare-up of CHR via the production of TNF-α. .COPYRGT. 2002 Elsevier Science Ireland Ltd. All rights reserved.

L11 ANSWER 12 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
2000:104519 Document No. 132:165114 Compound and method for the prevention and/or the **treatment** of **allergy**. Saint-Remy, Jean-Marie; Jacquemin, Marc (UCB S. A., Belg.). PCT Int. Appl. WO 2000006694 A2 20000210, 50 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-BE92 19990720. PRIORITY: EP 1998-870167 19980730.

AB The present invention is related to a compound for the prevention and/or the **treatment** of **allergy** consisting of: at least one allergen antigenic determinant which is recognized by a B cell or an antibody secreted by a B cell of a non-atopic individual to said allergen, and at least one antigenic determinant of an antigen different from said allergen which triggers T cell activation. Thus, peptides or proteins containing T cell epitope of tetanus toxoid and/or B cell epitope of Der p II allergen, or polypeptide containing T cell epitope of influenza A virus and B cell epitope of Der p I allergen were prepared for administration by gene transfer technol. through adenoviral vehicle, or by oral through food (e.g. acidified whey milk).

L11 ANSWER 13 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
2000:15329 Document No. 132:61291 Methods of expanding and selecting disease associated T-cells using antigen-presenting cells and disease associated antigens. Kaltoft, Keld; Agnholt, Jorgen (Den.). PCT Int. Appl. WO 2000000587 A1 20000106, 124 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-DK363 19990625. PRIORITY: DK 1998-848 19980626; DK 1998-895 19980701; US 1998-91684 19980702.

AB Methods of expanding and selecting disease associated T-cells, continuous T-cell lines as well as T-cell lines obtainable by these methods are disclosed. Furthermore, pharmaceutical compns. and vaccines comprising activated disease associated T-cell are disclosed. The uses of the T-cell and T-cell lines are numerous and include methods of diagnosis, methods for the **treatment**, alleviation or prevention of diseases associated with activation of T-cells, methods of testing the effect of medicaments against T-cell associated diseases, methods of detecting T-cell growth factors, methods of monitoring the response to **treatment**, alleviation or prevention of diseases associated with activation of T-cells, and methods of identifying disease associated antigens. Peripheral blood mononuclear cells were cultured with IL-2 and IL-4 and allostimulated with Psor-2 cells, a T-cell line from a patient with psoriasis vulgaris.

L11 ANSWER 14 OF 30 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:550226 The Genuine Article (R) Number: 334CP. Prolonged oral **treatment** with low doses of allergen conjugated to cholera toxin B subunit suppresses immunoglobulin E antibody responses in sensitized mice. Rask C; Holmgren J (Reprint); Fredriksson M; Lindblad M; Nordstrom I; Sun

J B; Czerkinsky C. GOTHENBURG UNIV, DEPT MED MICROBIOL & IMMUNOL, GULDHEDSGATAN 10, S-41346 GOTHENBURG, SWEDEN (Reprint); GOTHENBURG UNIV, DEPT MED MICROBIOL & IMMUNOL, S-41346 GOTHENBURG, SWEDEN; FAC MED PASTEUR, INSERM, U364, NICE, FRANCE. CLINICAL AND EXPERIMENTAL ALLERGY (JUL 2000) Vol. 30, No. 7, pp. 1024-1032. Publisher: BLACKWELL SCIENCE LTD. P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND. ISSN: 0954-7894. Pub. country: SWEDEN; FRANCE. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background Oral tolerance is a long recognized method for inducing systemic immunological tolerance. However, large doses of antigen and frequent administrations are often required. By linking the antigen to the nontoxic mucosa-binding B subunit of cholera toxin (CTB), the required amount can be dramatically reduced. We have previously shown that mucosal administration of small amounts of antigens coupled to CTB can suppress peripheral Th1 cell-reactivity and associated inflammatory immunopathology in both naive and systemically-immunized animals. Induction of oral tolerance by repeated feeding of relatively small doses of antigen has, in some cases been shown to involve the generation of regulatory Th2-like CD4(+) T cells, and hence could promote rather than suppress type I immunoglobulin (Ig) E-mediated allergic responses.

Objectives We examined whether oral prophylactic or therapeutic administration of a model allergen coupled to CTB would modulate allergen-specific IgE responses in high IgE responder Balb/c mice.

Methods Ovalbumin (OVA) was used as a model allergen. Mice were treated perorally with free or CTB-coupled OVA before or after systemic priming with alum-adsorbed OVA. Allergen-specific IgE levels in serum were measured with the passive cutaneous anaphylaxis test at various time-points.

Results Oral administration of a single low dose of CTB-linked OVA, prior to systemic sensitization and challenge with OVA, suppressed allergen-specific serum IgE antibody responses. **Treatment** with comparable doses of free OVA was much less effective. Most importantly, oral **treatment** with CTB-OVA conjugate could also suppress an already initiated IgE antibody response, but to achieve such a 'therapeutic effect', administration of multiple low doses of conjugate over a long time was required. Oral **treatment** with CTB-OVA conjugate could also effectively suppress antigen-specific Th1-mediated delayed-type hypersensitivity. Thus **treatment** with a CTB-conjugated model allergen can affect a broad range of T-cell-driven immune responses, even in antigen-experienced animals.

Conclusion These results may impact on the development of therapeutic vaccines against type I **allergies**.

L11 ANSWER 15 OF 30 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:803339 The Genuine Article (R) Number: 246TE. The modulation of B7.2 and B7.1 on B cells by immunosuppressive agents. Jirapongsananuruk O; Leung D Y M (Reprint). NATL JEWISH MED & RES CTR, DEPT PAEDIAT, 1400 JACKSON ST, DENVER, CO 80206 (Reprint); NATL JEWISH MED & RES CTR, DEPT PAEDIAT, DENVER, CO 80206; UNIV COLORADO, HLTH SCI CTR, DEPT PAEDIAT, DENVER, CO. CLINICAL AND EXPERIMENTAL IMMUNOLOGY (OCT 1999) Vol. 118, No. 1, pp. 1-8. Publisher: BLACKWELL SCIENCE LTD. P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND. ISSN: 0009-9104. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Several recent studies demonstrate that B7.2, but not B7.1, play an important role in allergic inflammation and IgE production. Agents that down-regulate B7.2 may therefore be of benefit for the **treatment** of Th2-driven allergic diseases. Our current study was carried our to investigate the effect of immunosuppressive agents, cyclosporin A (CsA) and dexamethasone, on B7.2 and B7.1 expression on B cells stimulated with the superantigen, toxic shock syndrome toxin-1 (TSST-1). The analysis of B7.2 and B7.1 on the same cells by flow cytometry demonstrated that TSST-1 up-regulated B7.2(+)B7.1(-) but not B7.1(+)B7.2(-) on B cells in a dose-dependent fashion. CsA and dexamethasone significantly downregulated

B7.2(+)B7.1(-) but up-regulated B7.2(-)B7.1(+) B cells in the presence or absence of TSST-1 (100 ng/ml). Interestingly, the combination of CsA and dexamethasone was much more potent in the inhibition of B7.2 expression than either of these agents alone. As CD40 is known to up-regulate B7.2 expression on B cells, the mechanism of B7.2 down-regulation by CsA and dexamethasone was further studied by investigating the effect of these agents on CD40 expression on B cells. TSST-1 significantly increased CD40 expression on B cells. However, the addition of CsA or dexamethasone significantly down-regulated CD40 expression. Anti-CD40 MoAb significantly reversed the effects of CsA or dexamethasone on B7.2 and B7.1 expression, suggesting that T cell engagement of CD40 plays a role in the mechanisms by which CsA and dexamethasone acts on B cells. These data demonstrate the modulatory effect of CsA and dexamethasone on B7.2 and B7.1 expression on B cells and the potential role of CD40 in mediating this effect.

L11 ANSWER 16 OF 30 EMBASE
on STN

1998105483 EMBASE A human-SCID mouse model for allergic immune responses: Bacterial superantigen enhances skin inflammation and suppresses IgE production. Herz U.; Schnoy N.; Borelli S.; Weigl L.; Kasbohrer U.; Daser A.; Wahn U.; Kottgen E.; Renz H.. Dr. H. Renz, Virchow-Klinikum the Humboldt-Univ., Institute of Clinical Chem./Biochem., Forschungshaus, Augustenburger Platz 1, 13353 Berlin, Germany. Journal of Investigative Dermatology 110/3 (224-231) 1998.
Refs: 41.
ISSN: 0022-202X. CODEN: JIDEAE. Pub. Country: United States. Language: English. Summary Language: English.

AB Chronic skin colonization with Staphylococcus aureus is a well-known feature in atopic dermatitis. The aim of this study was to develop a human- SCID mouse model to analyze the possible role of bacterial superantigens in human allergic immune responses under in vivo conditions. SCID mice were reconstituted with peripheral blood mononuclear cells (between 2 and 9 x 107 cells per mouse) from atopic dermatitis patients sensitized to house dust mite allergen (Der p). Total and Der p specific antibody production required the following conditions: (i) injection of Der p; (ii) presence of CD14+ antigen-presenting cells; and (iii) IL-4 as shown by the inhibitory effect of human soluble IL-4 receptor on immunoglobulin E production. This model was used to study the immunomodulatory effects of the superantigen staphylococcal **enterotoxin** B in comparision with Der p. In intraperitoneally reconstituted human-SCID mice, topical **treatment** was ineffective in inducing skin inflammation. Therefore, additionally to intraperitoneal transfer, peripheral blood mononuclear cells from atopic donors were also injected intradermally. Such reconstituted SCID mice were then exposed via the skin to either Der p, staphylococcal **enterotoxin** B, or a combination of both. Maximal effects on epidermal inflammation and dermal T cell infiltration were obtained with staphylococcal **enterotoxin** B and Der p. Staphylococcal **enterotoxin** B alone was less effective and Der p only stimulated dermal T cell infiltration. These findings support the hypothesis that bacterial superantigens can act as trigger factors in allergic skin inflammation.

L11 ANSWER 17 OF 30 EMBASE
on STN

1999093172 EMBASE Clinical management to Staphylococcus aureus using disinfectant therapy for atopic dermatitis. Sugimoto K.; Ishikawa N.; Ogawa A.. K. Sugimoto, Department of Pediatrics, Chiba Municipal Hospital, 827, Yahagi-cho, Chuo-ku, Chiba 260-0851, Japan. Skin Research 40/SUPPL. 20 (117-124) 1998.
Refs: 6.
ISSN: 0018-1390. CODEN: HIFUAG. Pub. Country: Japan. Language: Japanese. Summary Language: English; Japanese.

AB For the **treatment** of atopic dermatitis, we are drawing attention

to the high isolation rate of Staphylococcus aureus when starting disinfectant **treatment** combined with topical steroid therapies for the purpose of killing S. aureus. As a disinfectant, 10% povidone-iodine solution was used. At the end of the exposure time, povidone-iodine is to be thoroughly rinsed off. Disinfection using povidone-iodine is done twice to 4 times a day. As a result, we examined many patients in whom almost a complete remission was obtained even after short periods of therapy, though it had been difficult to obtain improvement by conventional **treatments**. In many patients, IgE values and reagin antibody titer decrease dramatically soon after starting **treatment**. We could examine duodenal biopsies in 5 patients. 3 out of 5 duodenal biopsy findings showed chronic duodenal inflammation with cell infiltrations, and other 2 biopsies showed moderate and mild duodenitis. Food antigen titers in RAST were dramatically decreased, but those of mite and house dust antigens were not changed with time. IgE levels and eosinophilia were prominently decreased. In many other cases, similar changes were observed. Although intestinal biopsy was not always carried out, it was assumed that chronic inflammation of the digestive tract may be improved in association with improvement of rashes even when no food elimination was made.

L11 ANSWER 18 OF 30 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
97:782064 The Genuine Article (R) Number: YB557. Small bowel review .1..
Thomson A B R (Reprint); Wild G. UNIV ALBERTA, DEPT MED, DIV GASTROENTEROL, NUTR & METAB RES GRP, 519 ROBERT NEWTON RES BLDG, EDMONTON, AB T6G 2C2, CANADA (Reprint). CANADIAN JOURNAL OF GASTROENTEROLOGY (SEP 1997) Vol. 11, No. 6, pp. 515-531. Publisher: MEDICARE PUBL INC, PULSUS GROUP INC. 2902 S SHERIDAN WAY, OAKVILLE ON L6J 7L6, CANADA. ISSN: 0835-7900. Pub. country: CANADA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Significant advances have been made in the study of the small bower. Part I of this two-part review of the small bowel examines carbohydrates, including brush border membrane hydrolysis and sugar transport; amino acids, dipeptides, proteins and food **allergy**, with a focus an glutamine, peptides and macromolecules, and nucleosides, nucleotides and polyamines; salt and water absorption, and diarrhea, including antidiarrheal therapy and oral rehydration **treatment**; lipids (digestion and absorption, fatty acid binding proteins, intracellular metabolism, lipoproteins and bile acids); and metals (eg, iron) and vitamins.

L11 ANSWER 19 OF 30 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
1996:243617 Document No.: PREV199698791746. Polyethylene glycol-modified IL-2 abrogates superantigen-induced anergy without affecting peripheral clonal deletion in vivo. Gonzalez-Garcia, Ana; Marchetti, Philippe; Castedo, Maria; Zamzami, Naoufal; Tarazona, Raquel; Martinez-A., Carlos; Kroemer, Guido [Reprint author]. CNRS-UPR 420, 19 rue Guy Moquet, BP 8, F-94801 Villejuif Cedex, France. Clinical Immunology and Immunopathology, (1996) Vol. 78, No. 3, pp. 215-222.
CODEN: CLIIAT. ISSN: 0090-1229. Language: English.
AB As compared with the native molecule, recombinant human interleukin-2 that is modified by covalently attached polyethylene glycol residues (IL-2-PEG) exhibits a markedly enhanced half-life in vivo, thus facilitating its biological evaluation. We have characterized the effect of IL-2-PEG on the Staphylococcus aureus **enterotoxin** B (SEB)-induced tolerance of peripheral SEB-reactive (V-beta-8+) T cells. **Treatment** with sublethal doses of IL-2-PEG does not modulate (inhibit or enhance) the SEB-triggered apoptosis and deletion of V-beta-8+ T cells. In contrast, in vivo **treatment** with IL-2-PEG partially abolishes the SEB-triggered anergy of V-beta-8+ T cells, i.e., the failure to proliferate in response to SEB in vitro. To abolish SEB-triggered anergy, IL-2-PEG must act for an extended period in vivo; short term **treatment** in vivo (2 days) or exposure of anergic T cells to IL-2

in vitro fails to reconstitute proliferative responses. Moreover, the effect of in vivo **treatment** with IL-2-PEG on lymphokine production by anergic T cells is partial. IL-2-PEG restores IL-4-dependent autocrine proliferation in response to SEB but does not reestablish defective IL-2 production. These data are compatible with the notion that IL-2 is a regulator of postdeletional rather than deletional T cell tolerance.

L11 ANSWER 20 OF 30 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
1995:401976 Document No.: PREV199598416276. Effect of staphylococcal **enterotoxin** B on rechallenge system of murine contact hypersensitivity. Natsuaki, Masaru; Abe, Kayoko; Kitano, Yukio. Dep. Dermatol., Hyogo Coll. Med., 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663, Japan. Skin Research, (1995) Vol. 37, No. 2, pp. 233-238.
CODEN: HIFUAG. ISSN: 0018-1390. Language: Japanese.

AB Staphylococcal **enterotoxins** have been known to be powerful stimulators of T lymphocytes in mouse and man and have recently been termed superantigens (SAg). SAg interact with particular V-beta regions of T cell receptor and major histocompatibility complex class II molecules, and activate a large number of T cells and accessory cells. Therefore, SAg may play important roles as immunomodulators. In this study, we investigated the effect of staphylococcal **enterotoxin** B (SEB) on rechallenge system of murine contact hypersensitivity reaction (CHR). Mice were sensitized with 2,4-dinitrofluorobenzene (DNFB) or 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (Ox) on day 0 and challenged with the same hapten on day 5. On day 33, specific hapten or SEB was injected intravenously and following ear swelling responses were nyl-2-oxazolin-5-one (Ox) on day 0 and challenged with the same hapten on day 5. On day 33, at 24 hours after SEB-injection and were non-specific to the hapten. When the supernatant of spleen cells cultured with SEB in vitro or recombinant murine tumor necrosis factor-alpha was injected on day 33, flare-up reactions were not found. These results indicate that SEB stimulate the immunological memory of CHR and may explain exacerbations of eczematous lesions associated with the secondary bacterial infection.

L11 ANSWER 21 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
95244932 EMBASE Document No.: 1995244932. Contact sensitizers modulate mechanisms of receptor-mediated endocytosis but not fluid-phase endocytosis in murine epidermal Langerhans cells. Becker D.; Lempertz U.; Enk A.; Saloga J.; Knop J.. Hautklinik, Johannes Gutenberg-Universitat, Langenbeckstrasse 1,55101 Mainz, Germany. Experimental Dermatology 4/4 I (211-217) 1995.
ISSN: 0906-6705. CODEN: EXDEEY. Pub. Country: Denmark. Language: English. Summary Language: English.

AB In order to define the influence of contact allergens on the fluid-phase endocytosis (FPE) of soluble molecules of murine epidermal Langerhans cells (LC), we studied the internalization of FITC-labeled bovine serum albumin (FITC-BSA), TRITC-iabeled dextrane (TRITC-DEX) as well as horseradish peroxidase by LC. A 3-parameter flow-cytometric technique was performed for quantification of internalized FITC-BSA in LC using quantum red-labeled reagents for detection of Ia-antigen expression by LC and propidium iodide for exclusion of dead cells from analysis. A temperature-dependent rapid accumulation of FITC-BSA was noticed in time-course studies reaching a plateau between 1 and 2 h of in vitro culture at 37°C. The quantity of FPE under stimulation with phorbol 12-myristate 13-acetate (PMA), concanavalin A (Con A), staphylococcal **enterotoxin** B (SEB) and contact sensitizers (DNFB, Kathon CG, K2Cr2O7) as well as the irritant SLS was determined. **Treatment** of LC with PMA and Con A resulted in a significant increase of total FITC-BSA uptake. The contact sensitizers as well as SEB and SLS failed to mediate augmented fluid-phase endocytosis. By use of the pH-insensitive

soluble marker, TRITC-DEX and a microscope photometer for evaluation these findings could be confirmed. This excluded any artificial influence of differences in pH values in endocytotic compartments which might have influenced the fluorescence intensity of the pH-sensitive fluorochrome FITC. For qualitative analysis of FPE, the intracellular distribution of internalized horseradish peroxidase in LC was studied. An aggregated pattern became apparent in untreated LC and did not change under stimulation with any of the substances used. This was in sharp contrast to a modulation of receptor-mediated endocytosis of antibody-crosslinked MHC class II molecules under the influence of contact sensitizers, and suggested that hapten-mediated endocytotic activation of LC was restricted to this mechanism of internalization.

L11 ANSWER 22 OF 30 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
1995:303914 Document No.: PREV199598318214. Type I interferon inhibition of superantigen stimulation: Implications for **treatment** of superantigen-associated disease. Soos, Jeanne M. [Reprint author]; Johnson, Howard M.. Dep. Microbiol. Cell Sci., Room 1019, Build. 981 Box 110700, Museum No Name Roads, Univ. Florida, Gainesville, FL 32611, USA. Journal of Interferon and Cytokine Research, (1995) Vol. 15, No. 1, pp. 39-45.
ISSN: 1079-9907. Language: English.

AB The interferons (IFNs) are a family of secretory glycoproteins possessing potent antiviral, antiproliferative, antimicrobial, and immunomodulatory activities. It has been shown that the IFNs and superantigens have an important effect on the course of certain autoimmune disorders, and thus we have examined the effect of the type I and type II IFNs on superantigen-induced stimulation. The type I IFNs, alpha, beta, and tau, inhibited induction of T cell proliferation by several staphylococcal **enterotoxin** superantigens; the type II IFN, gamma, was without effect. The type I IFNs inhibited T cell proliferation to the same extent, approximately 50% at 10-3 units of IFN/ml, and in a dose-dependent manner. Consistent with inhibition of proliferation, the type I IFNs also inhibited IL-2 production as well as levels of IL-2 receptor expression. Inhibition was not increased by using the IFNs in combination, suggesting that they inhibited proliferation by the same mechanism. IFNs alpha and beta, but not IFN-tau, were toxic to cells at high concentrations (gtoreq 10-4 units/ml). Thus, the mechanism by which type I IFNs inhibit cell proliferation differs from that associated with their toxic effects. A partial reduction of VP-specific superantigen-induced T cell expansion by type I IFNs was also demonstrated using flow cytometry. We recently showed that superantigens play an important role in the reactivation of experimental allergic encephalomyelitis. The potent antiproliferative activities of the type I IFNs strongly suggest the further study of their use as therapies for superantigen-associated diseases, such as multiple sclerosis and other autoimmune disorders, as well as toxic shock syndrome.

L11 ANSWER 23 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
1995:271411 Document No. 122:53910 Inhibition of the development of immediate hypersensitivity by staphylococcal **enterotoxin** B. Saloga, Joachim; Lack, Gideon; Bradley, Kathrine; Renz, Harald; Larsen, Gary; Leung, Donald Y. M.; Gelfand, Erwin W. (Dep. Pediatrics, Natl. Jewish Cent. Immunology, Denver, CO, USA). European Journal of Immunology, 24(12), 3140-7 (English) 1994. CODEN: EJIMAF. ISSN: 0014-2980. Publisher: VCH.

AB The authors investigated the ability of staphylococcal **enterotoxin** B (SEB) to modify the immediate hypersensitivity response induced in BALB/c mice following sensitization to ovalbumin (OVA), a response mediated by OVA-reactive Vβ8 T cells. Mice were sensitized by skin painting with OVA every second day over a period of 2 wk. SEB, a potent activator of Vβ8+ T cells, was administered at the same site where OVA was applied (skin of the lower abdomen) following two different protocols. In protocol (A) SEB was injected intradermally 1 day before

painting with OVA and on day 7; in protocol B, SEB was injected each time OVA was applied to the skin (eight times). SEB (but not SEA) altered the development of immediate hypersensitivity to OVA, as demonstrated by the reduction in allergen-specific IgE, decreased OVA-specific immediate skin test responsiveness, and prevented the development of increased airway responsiveness after bronchial challenge with OVA. Injections of SEB did not alter the proliferative responses of local draining lymph node cells or spleen mononuclear cells to OVA, indicating that administration of SEB did not inhibit the sensitization to OVA, but shifted the immune response away from an immediate type response (IgE/IgG1) to IgG2a, IgG2b and IgG3. Although both protocols of SEB **treatment** did not lead to a major deletion of the Vβ8 T cell population, they did reduce the proliferative response of Vβ8+ T cells to OVA. These data indicate that the bacterial toxin SEB is capable of modifying the immediate hypersensitivity response induced by OVA by altering the functional capacity of antigen-reactive Vβ8 T cells.

L11 ANSWER 24 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
1994:555532 Document No. 121:155532 The model of arthritis induced by superantigen in mice. Nagai, Hiroichi; Takaoka, Yuko; Kamada, Hiroyuki; Mori, Hiroshi (Dep. Pharmacology, Gifu Pharmaceutical Univ., Gifu, 502, Japan). Life Sciences, 55(12), PL233-PL237 (English) 1994. CODEN: LIFSAK. ISSN: 0024-3205.

AB S.c. injection of Staphylococcal **enterotoxin** B (SEB) produced by Staphylococcus aureus, caused severe arthritis in DBA/1J mice which had been previously immunized with bovine type II collagen. The severity of this arthritis was dose dependent and prolonged joint inflammation with erosion of bone was observed Anti-type II collagen antibodies were detected in the serum of arthritic mice. Effector T cells against type II collagen were also detected by delayed type hypersensitivity in the skin. Moreover, a significant decrease in the ratio between T cells and B cells and an increase in the ratio between CD4+ cells and CD8+ cells was observed in spleen cells from arthritic mice. Prednisolone suppresses the induction and development of clin. signs of arthritis in mice. This evidence suggests that this exptl. arthritis model may provide a means to examine the role of superantigens and the efficacy of pharmacol. agents for the **treatment** of rheumatoid arthritis.

L11 ANSWER 25 OF 30 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 1
91138419 EMBASE Document No.: 1991138419. Functional inactivation of Dermatophagoides spp. (house dust mite) reactive human T-cell clones. O'Hehir R.E.; Aguilar B.A.; Schmidt T.J.; Gollnick S.O.; Lamb J.R.. Department of Immunology, Wright-Fleming Institute, St. Mary's Hosp. Med. School, Norfolk Place,London W2 1PG, United Kingdom. Clinical and Experimental Allergy 21/2 (209-215) 1991.
ISSN: 0954-7894. CODEN: CLEAEN. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Staphylococcal **enterotoxins** are able both to stimulate powerful polyclonal proliferative responses and to induce non-responsiveness of T lymphocytes expressing the appropriate T-cell antigen receptor Vβ gene products. T-cell clones representative of the human response to house dust mite were identified that express either Vβ3 or Vβ6 gene products. The specificity of the latter was confirmed by serology. Pre-**treatment** of cloned Vβ3+ T cells with the Staphylococcus aureus **enterotoxins** B or C1 rendered them non-responsive to immunogenic challenge with their natural ligand, while retaining responsiveness to exogenous IL-2. Similarly, exposure of the Vβ6+ dust mite reactive T cells to the staphylococcal **enterotoxin** of the appropriate specificity, SEE, induced specific energy. The development of non-responsiveness was associated with changes in the T-cell phenotypes. Downregulation of the T-cell receptor, Ti-CD3, was paralleled by enhanced expression of both CD2 and the IL-2 receptor, CD25.

Differential comodulation of CD4 and Ti-CD3 suggested that for some T cells CD4 may form part of the specific antigen recognition structure. Toxicity of the staphylococcal **enterotoxins** may be removed by chemical modification, thus their ability functionally to inactivate subpopulations of T cells expressing antigen-specific receptors with shared characteristics may be of potential value in the regulation of allergic diseases if the diversity of the T-cell repertoire proves to be limited.

L11 ANSWER 26 OF 30 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
1991:219968 Document No.: PREV199140105803; BR40:105803. FUNCTIONAL INACTIVATION OF HOUSE DUST MITE SPECIFIC HUMAN CD4-T CELL CLONES. O'HEHIR R E [Reprint author]; LAMB J R. LONDON, UK. Journal of Allergy and Clinical Immunology, (1991) Vol. 87, No. 1 PART 2, pp. 163.
Meeting Info.: FORTY-SEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF ALLERGY AND IMMUNOLOGY, SAN FRANCISCO, CALIFORNIA, USA, MARCH 1-6, 1991. J ALLERGY CLIN IMMUNOL.
CODEN: JACIBY. ISSN: 0091-6749. Language: ENGLISH.

L11 ANSWER 27 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
1991:512247 Document No. 115:112247 Production and isolation of guinea pig IgE antibody. Karol, Meryl; Jin, Ruzhi; Bennedsen, Mark; Vaughan, Frank (Grad. Sch. Public Health, Univ. Pittsburgh, Pittsburgh, PA, 15261, USA). Journal of Immunological Methods, 139(1), 123-34 (English) 1991. CODEN: JIMMBG. ISSN: 0022-1759.
AB Igs of the IgE and IgG classes have been causally associated with hypersensitivity reactions in man and in numerous animal species including mice, rats, and guinea pigs. The use of the guinea pig as an animal model for both pulmonary and dermal hypersensitivity reactions, and the recent recognition of the importance of IgE antibodies in both early- and late-onset hypersensitivity responses, has heightened interest in production, separation, and isolation of this Ig class from the guinea pig. IgE antibodies were produced by **treatment** of strain 13 guinea pigs with cyclophosphamide followed by injection with Staphylococcus aureus **enterotoxin**. Serum was obtained and the globulin fraction isolated by addition of caprylic acid then ammonium sulfate. Igs were separated into classes using fast protein liquid chromatog. employing a Mono Q column and a linear gradient of 0.01-0.3 M Na,K phosphate buffer, pH 7.5 (buffer B). IgG eluted in 2 major peaks. IgG2 was not retained on the column and emerged with the starting buffer; IgG1 was eluted with 15-20% buffer B. IgE, detected as heat labile homocytotrophic antibody, was found in the fraction eluting with 30-35% buffer B. The elution profile of the guinea pig Igs was predicted from the pattern obtained with Ig classes from other species. This chromatog. procedure enabled rapid isolation of Ig classes from guinea pig sera and effectively separated IgG1 from IgE, the 2 classes associated with hypersensitivity reactions.

L11 ANSWER 28 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
1991:115084 Document No. 114:115084 Antiallergy agents containing allergens and adjuvants and antiallergy agents containing allergen-adjuvant complexes. Watanabe, Naohiro (Japan). Jpn. Kokai Tokkyo Koho JP 02235823 A2 19900918 Heisei, 5 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1989-54887 19890309.
AB Antiallergy agents, which are useful for **treatment** of type I **allergy**, e.g. asthma and allergic rhinitis, and have low toxicity, contain (1) allergens and adjuvants stimulating production of IgA against the allergens; or (2) allergens bonded with the adjuvants (via spacers). Nasal administration of 10 μg ovalbumin and 1.0 μg cholera toxin produced antiovalbumin IgA in mice, vs. none, without the toxin.

L11 ANSWER 29 OF 30 CAPLUS COPYRIGHT 2004 ACS on STN
1987:634622 Document No. 107:234622 Cysteinyl leukotrienes as mediators of

staphylococcal **enterotoxin** B in the monkey. Scheuber, P. H.; Denzlinger, C.; Wilker, D.; Beck, G.; Keppler, D.; Hammer, D. K. (Biochem. Inst., Univ. Freiburg, Freiburg, Fed. Rep. Ger.). European Journal of Clinical Investigation, 17(5), 455-9 (English) 1987. CODEN: EJCIB8. ISSN: 0014-2972.

AB The role of cysteinyl leukotrienes (LTs) in the action of staphylococcal **enterotoxin** B (SEB) was investigated in unsensitized monkeys using inhibitors of prostanoid synthesis and LT action and by measuring generation of LT in vivo. LY 171883, a selective LTD4/LTE4 receptor antagonist, was highly efficient in inhibiting immediate-type hypersensitivity reactions in the skin and protecting against the emetic response provoked by SEB in a concentration-dependent manner. Inhibition of prostanoid formation by pretreatment of monkeys with indomethacin or aspirin did not influence SEB responses. Based on chromatog. and RIA, the generation of endogenous cysteinyl LTs was demonstrated in vivo. The concentration of LTE4, the major biliary cysteinyl LT detected, increased 10-fold and a novel cysteinyl LT metabolite in urine indicated strongly enhanced LT generation upon challenge with SEB. Cysteinyl LTs are important mediators in the pathophysiol. of SEB-induced enteric intoxication. Therefore, cysteinyl LT antagonists may be of therapeutic value in the **treatment** of this intestinal disorder.

L11 ANSWER 30 OF 30 MEDLINE on STN DUPLICATE 2

85070398. PubMed ID: 6391290. Research and development of infant formulae with reduced allergenic properties. Pahud J J; Schwarz K. Annals of allergy, (1984 Dec) 53 (6 Pt 2) 609-14. Ref: 33. Journal code: 0372346. ISSN: 0003-4738. Pub. country: United States. Language: English.

AB Infant formulae based on hydrolyzed proteins or elemental diets offer the best **treatment** of cow's milk **allergy** whenever exclusive breast-feeding is not possible. In situations with a family history of atopy, formulae using other protein sources such as soya or chicken meat can also be a good preventive measure. The food industry needs reliable research methods for the evaluation of every new option before considering clinical trials. Allergenicity of cow's milk proteins was evaluated by the induction of mouse monoclonal reagins and also by oral administration of milk preparations to mice and guinea pigs. Animals initially raised on commercial diets containing about 1% milk whey could not be sensitized. Maintenance of a milk-free diet from pregnancy until weaning, and feeding milk in a liquid form led to an optimal sensitization of the guinea pigs. These animals suffered systemic anaphylaxis and their sera sensitized skin in virgin hosts. Under optimal conditions, while giving liquid preparations to drink, a considerable proliferation of the milk flora occurred. As no mucosal alterations could be detected, primary gut damage due to infection was probably not the triggering factor for oral sensitization. Bacterial products (e.g., endotoxins, **enterotoxins**) could stimulate the gut response towards milk proteins, either due to an adjuvant effect or to increased mucosal permeability. Microbial contamination of milk is practically unavoidable and it can generally induce biologic activity, e.g., fresh milk regularly gives a positive limulus test for endotoxin by the time it is consumed or processed. Reduction of bacterial contaminants by milk protective factors might help to prevent oral sensitization.(ABSTRACT TRUNCATED AT 250 WORDS)

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=> s l2 and tolerance
L12       1480 L2 AND TOLERANCE

=> s l12 and "CtxB"
L13          0 L12 AND "CTXB"

=> s "CtxB"
L14        411 "CTXB"
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=> s l14 and type I allergy
L15          0 L14 AND TYPE I ALLERGY

=> s l14 and allergy
L16          1 L14 AND ALLERGY

=> d l16 cbib abs

L16  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2004 ACS on STN
2000:814337   Document No. 133:361908  Bacteriophage isolated from bacterial
     genomes and extrachromosomal elements and methods of use thereof.
     Karaolis, David K. R. (University of Maryland, Baltimore, USA).  PCT Int.
     Appl. WO 2000067784 A1 20001116, 59 pp.  DESIGNATED STATES: W:  AE, AL,
     AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM,
     EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP,
     KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ,
     PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,
     UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF,
     BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU,
     MC, ML, MR, NE, NL, PT, SE, SN, TD, TG.  (English).  CODEN: PIXXD2.
     APPLICATION: WO 2000-US12580 20000510.  PRIORITY: US 1999-PV133373
     19990510.
AB   The present invention relates to compns., methods, processes, etc.,
     relating to bacteriophage which are encoded by chromosome, plasmids, or an
     extrachromosomal element of bacteria.  The bacteriophage of the present
     invention are preferably encoded by pathogenicity islands in chromosomes
     or plasmids of pathogenic bacteria.  The bacteriophage can be utilized as
     a pharmaceutical composition, e.g., to elicit an immune response, e.g., for the
     purpose of producing antibodies, as vaccines and vaccine vectors to
     regulate the immune system, e.g., for the prevention and treatment of
     allergy, disease, and other pathol. conditions.  The invention
     finds addnl. utility in systems and methods for the detection of pathogens
     comprising bacteriophage and a system and method for the environmental
     eradication of pathogenic microorganisms.


=> s composition
L17    2899736 COMPOSITION

=> s l17 and allergen
L18       2213 L17 AND ALLERGEN

=> s l18 and unconjugate
L19          0 L18 AND UNCONJUGATE

=> s l18 and type I
L20         53 L18 AND TYPE I

=> s l20 and mucosa binding agent
L21          0 L20 AND MUCOSA BINDING AGENT

=> s mucosa binding agent
L22          0 MUCOSA BINDING AGENT

=> s GM1 ganglioside receptor
L23        104 GM1 GANGLIOSIDE RECEPTOR

=> s l23 and binding agent
L24          0 L23 AND BINDING AGENT

=> s oral tolerance
L25       4942 ORAL TOLERANCE
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=> s l25 and allergy
L26 614 L25 AND ALLERGY

=> s l26 and cholera toxin B subunit
L27 8 L26 AND CHOLERA TOXIN B SUBUNIT

=> dup remove l27
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L28 4 DUP REMOVE L27 (4 DUPLICATES REMOVED)

=> d l28 1-4 cbib abs

L28 ANSWER 1 OF 4 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
2003192785 EMBASE Mucosal adjuvants and anti-infection and anti-immunopathology vaccines based on cholera toxin, **cholera toxin B subunit** and CpG DNA. Holmgren J.; Harandi A.M.; Czerkinsky C.. J. Holmgren, Department of Medical Microbiology, Goteborg Univ. Vacc. Res. Institute, Goteborg University, Guldhedsgatan 10A, SE-413 46 Goteborg, Sweden. jan.holmgren@microbio.gu.se. Expert Review of Vaccines 2/2 (205-217) 2003.
Refs: 64.
ISSN: 1476-0584. CODEN: ERVXAX. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB The mucosal immune system consists of an integrated network of lymphoid cells that work in concert with innate host factors to promote host defence. Mucosal immunization can be used both to protect the mucosal surfaces against colonization and invasion by microbial pathogens and to provide a means for immunological treatment of selected autoimmune, allergic or infectious-immunopathological disorders through the induction of antigen-specific tolerance. The development of mucosal vaccines, whether for prevention of infectious diseases or for **oral tolerance** immunotherapy, requires efficient antigen delivery and adjuvant systems. Significant progress has recently been made to generate partly or wholly detoxified derivatives of cholera toxin (including the completely nontoxic **cholera toxin B subunit**) and the closely related Escherichia coli heat-labile enterotoxin, with retained adjuvant activity. **Cholera toxin B subunit** is a protective component of a widely registered oral vaccine against cholera, and has proven to be a promising vector for either giving rise to anti-infective immunity or for inducing peripheral anti-inflammatory tolerance to chemically or genetically linked foreign antigens administered mucosally. Promising advances have also recently been made In the design of efficient mucosal adjuvants based on bacterial DNA that contains CpG-motifs and various imidazoquinoline compounds binding to different Toll-like receptors on mucosal antigen-presenting cells.

L28 ANSWER 2 OF 4 MEDLINE on STN DUPLICATE 1
2000385105. PubMed ID: 10848926. Prolonged oral treatment with low doses of allergen conjugated to **cholera toxin B subunit** suppresses immunoglobulin E antibody responses in sensitized mice. Rask C; Holmgren J; Fredriksson M; Lindblad M; Nordstrom I; Sun J B; Czerkinsky C. (Department of Medical Microbiology and Immunology, Goteborg University, Goteborg, Sweden.) Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology, (2000 Jul) 30 (7) 1024-32. Journal code: 8906443. ISSN: 0954-7894. Pub. country: ENGLAND: United Kingdom. Language: English.
AB BACKGROUND: **Oral tolerance** is a long recognized method for inducing systemic immunological tolerance. However, large doses of antigen and frequent administrations are often required. By linking the

antigen to the nontoxic mucosa-binding B subunit of cholera toxin (CTB), the required amount can be dramatically reduced. We have previously shown that mucosal administration of small amounts of antigens coupled to CTB can suppress peripheral Th1 cell-reactivity and associated inflammatory immunopathology in both naive and systemically-immunized animals. Induction of **oral tolerance** by repeated feeding of relatively small doses of antigen has, in some cases been shown to involve the generation of regulatory Th2-like CD4+ T cells, and hence could promote rather than suppress type I immunoglobulin (Ig) E-mediated allergic responses. OBJECTIVES: We examined whether oral prophylactic or therapeutic administration of a model allergen coupled to CTB would modulate allergen-specific IgE responses in high IgE responder Balb/c mice. METHODS: Ovalbumin (OVA) was used as a model allergen. Mice were treated perorally with free or CTB-coupled OVA before or after systemic priming with alum-adsorbed OVA. Allergen-specific IgE levels in serum were measured with the passive cutaneous anaphylaxis test at various time-points. RESULTS: Oral administration of a single low dose of CTB-linked OVA, prior to systemic sensitization and challenge with OVA, suppressed allergen-specific serum IgE antibody responses. Treatment with comparable doses of free OVA was much less effective. Most importantly, oral treatment with CTB-OVA conjugate could also suppress an already initiated IgE antibody response, but to achieve such a 'therapeutic effect', administration of multiple low doses of conjugate over a long time was required. Oral treatment with CTB-OVA conjugate could also effectively suppress antigen-specific Th1-mediated delayed-type hypersensitivity. Thus treatment with a CTB-conjugated model allergen can affect a broad range of T-cell-driven immune responses, even in antigen-experienced animals. CONCLUSION: These results may impact on the development of therapeutic vaccines against type I **allergies**.

L28 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
1999:52433 Document No. 130:250778 **Oral tolerance** and anti-pathological vaccines. Czerkinsky, C.; Sun, J.-B.; Holmgren, J. (INSERM Unit 364, Cellular and Molecular Immunology, Faculte de Medecine-Pasteur, Nice, 06107, Fr.). Current Topics in Microbiology and Immunology, 236(Defense of Mucosal Surfaces: Pathogenesis, Immunity and Vaccines), 79-91 (English) 1999. CODEN: CTMIA3. ISSN: 0070-217X. Publisher: Springer-Verlag.

AB A review with 50 refs. Topics discussed include mechanism of induction and expression of peripheral tolerance after mucosal delivery of antigens; mucosal immunotherapy; **cholera toxin B subunit** as a mucosal carrier-immunomodulating system for anti-pathol. vaccination; treatment of organ-specific autoimmune diseases; prevention of graft rejection and type I **allergies**; and mucosal vaccines for simultaneous induction of anti-infectious and anti-pathol. immunity.

L28 ANSWER 4 OF 4 MEDLINE on STN
93050830. PubMed ID: 1426671. Oral administration of immunomodulators and the mucosal immune system. Revillard J P; Cozon G; Czerkinsky C. (Laboratoire d'Immunologie, INSERM U80 CNRS URA 1177 UCBL, Hopital E. Herriot, Lyon, France.) Developments in biological standardization, (1992) 77 31-7. Ref: 25. Journal code: 0427140. ISSN: 0301-5149. Pub. country: Switzerland. Language: English.

AB Orally administered antigens reach the lymphoid tissue in Peyer's patches in the gut where they initiate an immune response with clonal expansion of antigen-specific T and B cells. Activated T cells migrate through lymph and blood to intestinal epithelium (intra-epithelial leukocytes) whereas activated B cells migrate to the lamina propria, other mucosae and exocrine glands where they differentiate into plasma cells secreting polymeric IgA1 or IgA2. These antibodies are transported across the epithelial cells after binding to a poly-Ig receptor, then excreted in the lumen as secretory IgA. Reciprocal interactions have been demonstrated

between lymphoid and epithelial cells in the mucosae. Oral administration of antigens in different experimental models may induce the production of secretory antibodies and/or systemic unresponsiveness with suppression of delayed-type hypersensitivity or specific IgG and IgE antibody production or both. New strategies are currently being explored for the development of oral vaccines using recombinant antigens or viral vectors (e.g. pox-viruses, vaccinia virus, **cholera toxin B subunit** etc.). Conversely, immunomodulating compounds or procedures which could enhance specific **oral tolerance** in association with antigen would have considerable therapeutic applications in auto-immune diseases and **allergy**.

=> s l26 and cholera toxin
L29 34 L26 AND CHOLERA TOXIN

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PROCESSING COMPLETED FOR L29
L30 18 DUP REMOVE L29 (16 DUPLICATES REMOVED)

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L38 NOT FOUND
The L-number entered has not been defined in this session, or it has been deleted. To see the L-numbers currently defined in this session, enter DISPLAY HISTORY at an arrow prompt (=>).

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L30 ANSWER 1 OF 18 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:430403 The Genuine Article (R) Number: 679DA. Genetic susceptibility to food **allergy** is linked to differential T(H)2-T(H)1 responses in C3H/HeJ and BALB/c mice. Morafo V (Reprint); Srivastava K; Huang C K; Kleiner G; Lee S Y; Sampson H A; Li X M. CUNY Mt Sinai Sch Med, Dept Pediat, 1 Gustave L Levy Pl, New York, NY 10029 USA (Reprint); CUNY Mt Sinai Sch Med, Dept Pediat, New York, NY 10029 USA. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (MAY 2003) Vol. 111, No. 5, pp. 1122-1128. Publisher: MOSBY, INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318 USA. ISSN: 0091-6749. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Background: Although food **allergy** is a serious health problem in westernized countries, factors influencing the development of food **allergy** are largely unknown. Appropriate marine models of food **allergy** would be useful in understanding the mechanisms underlying food **allergy** in human subjects.

Objective: We sought to determine the susceptibility of different strains of mice to food hypersensitivity.

Methods: C3H/HeJ and BALB/c mice were sensitized to cow's milk (CM) or peanut by means of intragastric administration, with **cholera toxin** as a mucosal adjuvant. Mice were then challenged with CM or peanut Antigen-specific IgE levels, anaphylactic symptoms, plasma histamine levels, and splenocyte cytokine profiles of these 2 strains were compared.

Results: CM-specific IgE levels were significantly increased only in the C3HMeJ strain, 87% of which exhibited systemic anaphylactic reactions accompanied by significantly increased plasma histamine levels in response to challenge. BALB/c mice exhibited no significant CM-specific IgE response, increased plasma histamine levels, or anaphylactic symptoms. After peanut challenge, 100% of peanut-sensitized C3H/HeJ mice exhibited high levels of peanut-specific IgE and anaphylactic symptoms. In contrast, no hypersensitivity reactions were detected in BALB/c mice, despite the presence of significant serum peanut-specific IgE levels. Splenocytes from CM- and peanut-sensitized C3H/HeJ mice exhibited significantly increased IL-4 and IL-10 secretion, whereas splenocytes from BALB/c mice exhibited

significantly increased IFN-gamma secretion.
Conclusion: induction of food-induced hypersensitivity reactions in mice is strain dependent, with C3H/HeJ mice being susceptible and BALB/c mice being resistant. This strain-dependent susceptibility to food **allergy** is associated with differential T(H)2-T(H)1 responses after intragastric food allergen sensitization.

L30 ANSWER 2 OF 18 MEDLINE on STN DUPLICATE 1
2003583198. PubMed ID: 14646386. Low-dose **oral tolerance** due to antigen in the diet suppresses differentially the **cholera toxin**-adjuvantized IgE, IgA and IgG response. Christensen Hanne R; Kjaer Tanja M R; Frokiaer Hanne. (BioCentrum-DTU, Biochemistry and Nutrition, Technical University of Denmark, Kgs Lyngby, Denmark.. hrc@biocentrum.dtu.dk) . International archives of allergy and immunology, (2003 Nov) 132 (3) 248-57. Journal code: 9211652. ISSN: 1018-2438. Pub. country: Switzerland. Language: English.
AB BACKGROUND: **Cholera toxin** (CT) is used as a mucosal adjuvant amongst other applications for studying food **allergy** because oral administration of antigen with CT induces an antigen-specific type 2 response, including IgE and IgA production. Previously established **oral tolerance** due to antigen in the diet may radically impact on the CT-adjuvantized immune response. The present study served to evaluate the effect of previously established low-dose **oral tolerance** on the CT-adjuvantized immune response towards a food antigen. METHODS: Mice fed a diet containing microgram levels of the soy protein Kunitz soy-trypsin inhibitor (KSTI) (F0 mice) and mice fed a soy-free diet (F2 mice) were orally immunized with KSTI and CT. KSTI-specific serum IgG1, IgG2a, IgA and IgE and fecal IgA were monitored. KSTI-stimulated cell proliferation and interleukin (IL)-6 production were determined. RESULTS: The anti-KSTI IgE and IgA responses in the F0 mice were substantially suppressed, while the IgG1 and IgG2a responses were not suppressed after five oral immunizations. The response suppression tended to decline with increasing numbers of immunizations suggesting that the suppression could be overcome by multiple immunizations. However, cell proliferation and IL-6 production were clearly suppressed even after five immunizations. CONCLUSIONS: Priorly established low-dose **oral tolerance** considerably suppressed the CT-adjuvantized KSTI-specific IgE, IgA and cellular immune response but only weakly and transiently the IgG response. The results revealed that low-dose **oral tolerance** includes the mucosal IgA response and that CT, albeit mediating an antigen-specific response, does not fully abrogate previously established **oral tolerance**.

L30 ANSWER 3 OF 18 EMBASE
on STN
2003192785 EMBASE Mucosal adjuvants and anti-infection and anti-immunopathology vaccines based on **cholera toxin**, **cholera toxin** B subunit and CpG DNA. Holmgren J.; Harandi A.M.; Czerkinsky C.. J. Holmgren, Department of Medical Microbiology, Goteborg Univ. Vacc. Res. Institute, Goteborg University, Guldhedsgatan 10A, SE-413 46 Goteborg, Sweden. jan.holmgren@microbio.gu.se. Expert Review of Vaccines 2/2 (205-217) 2003.
Refs: 64.
ISSN: 1476-0584. CODEN: ERVXAX. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB The mucosal immune system consists of an integrated network of lymphoid cells that work in concert with innate host factors to promote host defence. Mucosal immunization can be used both to protect the mucosal surfaces against colonization and invasion by microbial pathogens and to provide a means for immunological treatment of selected autoimmune, allergic or infectious-immunopathological disorders through the induction

of antigen-specific tolerance. The development of mucosal vaccines, whether for prevention of infectious diseases or for **oral tolerance** immunotherapy, requires efficient antigen delivery and adjuvant systems. Significant progress has recently been made to generate partly or wholly detoxified derivatives of **cholera toxin** (including the completely nontoxic **cholera toxin** B subunit) and the closely related Escherichia coli heat-labile enterotoxin, with retained adjuvant activity. **Cholera toxin** B subunit is a protective component of a widely registered oral vaccine against cholera, and has proven to be a promising vector for either giving rise to anti-infective immunity or for inducing peripheral anti-inflammatory tolerance to chemically or genetically linked foreign antigens administered mucosally. Promising advances have also recently been made In the design of efficient mucosal adjuvants based on bacterial DNA that contains CpG-motifs and various imidazoquinoline compounds binding to different Toll-like receptors on mucosal antigen-presenting cells.

L30 ANSWER 4 OF 18 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2003:572672 Document No.: PREV200300571012. INDUCTION OF UVEITIS BY BREAKING **ORAL TOLERANCE** TO A NUTRIONAL ANTIGEN. Wildner, G. [Reprint Author]; Diedrichs-Moehring, M. [Reprint Author]. Dept of Ophthalmology, Ludwig-Maximilians Univ, Munich, Germany. ARVO Annual Meeting Abstract Search and Program Planner, (2003) Vol. 2003, pp. Abstract No. 4303. cd-rom.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, FL, USA. May 04-08, 2003. Association for Research in Vision and Ophthalmology.
Language: English.

AB Purpose: Exogenous antigens such as infectious agents mimicking autoantigens are suspected triggers of autoimmune diseases by initiating defensive immune responses. Nutritional antigens are normally tolerated by the immune system. However, under certain conditions (e.g. concomitant infections) food antigens can be attacked by the immune system as well, leading to food **allergies** or even to autoimmune diseases. Here we demonstrate the induction of EAU by bovine milk casein, a common food antigen, which can mimic retinal S-Antigen peptide. Methods: Lewis rats were subcutanously immunized with retinal S-Ag-peptide (PDSAg), a peptide from bovine casein (Cas) or the whole casein protein, both emulsified in CFA, to induce uveitis. Rat T cell lines specific for these antigens were analyzed in vitro for crossreactivity and in vivo for pathogenicity (adoptive transfer). We furthermore tested the ability of casein and Cas to elicit **oral tolerance** to PDSAg-induced uveitis. To prove the concept of breaking **oral tolerance** as an initiating event of the autoimmune response we cofed rats with casein, S-Ag, as well as the respective peptides and **Cholera toxin.** We furthermore tested sera and peripheral blood lymphocytes from uveitis patients and healthy donors for casein-specific responses. Results: Immunization with casein peptide and casein protein induced uveitis in up to 75% of rats. Casein and Cas specific T cell lines were crossreactive with S-Antigen peptide and uveitogenic after adoptive transfer in 25-65% of rats. Peptide Cas was orally tolerogenic, whereas casein failed to prevent PDSAg-induced uveitis.Interestingly, following concomitant feeding of casein (but not Cas and PDSAg) with **Cholera toxin** 75% of rats developed uveitis. Patients with iritis had significantly elevated antibody ($p<0.05$) and T cell responses to casein, Cas and S-Ag compared to healthy donors. Conclusions: Breaking **oral tolerance** to bovine casein, a common food antigen in industrialized countries, might initiate an immune response that crossreacts with retinal S-Antigen and thus lead to autoimmune uveitis.

L30 ANSWER 5 OF 18 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2002:632825 The Genuine Article (R) Number: BU76Q. **Oral tolerance**, systemic immunoregulation, and autoimmunity. Strobel S (Reprint). Inst Child Hlth, Immunobiol Unit, 30 Guilford St, London WC1N 1EH, England (Reprint); Great Ormond St Hosp Children, London WC1N 1EH, England. IMMUNOLOGY OF DIABETES: AUTOIMMUNE MECHANISMS AND THE PREVENTION AND CURE OF TYPE 1 DIABETES (1 AUG 2002) Vol. 958, pp. 47-58. Publisher: NEW YORK ACAD SCIENCES. 2 EAST 63RD ST, NEW YORK, NY 10021 USA. ISSN: 0077-8923. Pub. country: England. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Convincing clinical and experimental evidence suggests that the disturbance of important immunoregulatory and suppressive immunological events induced after oral (mucosal) antigen exposure (**oral tolerance**) may lead to allergic and autoimmune diseases. Within a variety of factors, age of the host and timing of antigen (food) administration are important characteristics in the development of food allergic disease. Induction of tolerance is seen as a Th2 skewed response, which on one side may prevent harmful mucosal immune reactions but on the other side may contribute to adverse responses in the susceptible individual. The primary mechanisms by which tolerance may be mediated include deletion, anergy, suppression, "ignorance," and apoptosis. Cell-mediated delayed hypersensitivity reactions (Th1), which are implicated in the development of autoimmune and gastrointestinal diseases, are particularly well suppressed. Regulatory events after mucosal exposure of antigen are not well characterized and remain controversial. The balance between tolerance (suppression) and sensitization (priming) is dependent on several factors, such as: (a) genetic background, (b) nature and dose of antigen, (c) frequency of administration, (d) age at first antigen exposure, (e) immunological status of the host, (f) antigen transmission via breast milk, and others. Overall there is evidence in rodents that multiple low-dose feeds are more likely to induce regulatory cytokines (e.g., TGF-beta, IL-10, IL-4) in part secreted by CD4(+)CD25(+) T regulatory cells. Despite the powerful suppressive effects of oral autoantigen exposure observed in experimental models of autoimmune diseases (including bystander suppression), their translation into clinical trials of autoimmune diseases has not yet yielded the expected beneficial results.

L30 ANSWER 6 OF 18 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:93961 The Genuine Article (R) Number: 395YE. Probiotics: effects on immunity. Isolauri E (Reprint); Sutas Y; Kankaanpaa P; Arvilommi H; Salminen S. Univ Turku, Dept Pediat, FIN-20520 Turku, Finland (Reprint); Univ Turku, Dept Biochem & Food Chem, FIN-20520 Turku, Finland; Natl Publ Hlth Inst, Turku, Finland. AMERICAN JOURNAL OF CLINICAL NUTRITION (FEB 2001) Vol. 73, No. 2, Supp. [S], pp. 444S-450S. Publisher: AMER SOC CLINICAL NUTRITION. 9650 ROCKVILLE PIKE, SUBSCRIPTIONS, RM L-3300, BETHESDA, MD 20814-3998 USA. ISSN: 0002-9165. Pub. country: Finland. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The gastrointestinal tract functions as a barrier against antigens from microorganisms and food. The generation of immunophysiologic regulation in the gut depends on the establishment of indigenous microflora. This has led to the introduction of never therapeutic interventions based on the consumption of cultures of beneficial live microorganisms that act as probiotics. Among the possible mechanisms of probiotic therapy is promotion of a nonimmunologic gut defense barrier, which includes the normalization of increased intestinal permeability and altered gut microecology. Another possible mechanism of probiotic therapy is improvement of the intestine's immunologic barrier, particularly through intestinal immunoglobulin A responses and alleviation of intestinal inflammatory responses, which produce a gut-stabilizing effect. Many probiotic effects are mediated through immune regulation, particularly through balance control of proinflammatory and antiinflammatory cytokines. These data show that probiotics can be used as innovative tools to

alleviate intestinal inflammation, normalize gut mucosal dysfunction, and down-regulate hypersensitivity reactions. More recent data show that differences exist in the immunomodulatory effects of candidate probiotic bacteria. Moreover, distinct regulatory effects have been detected in healthy subjects and in patients with inflammatory diseases. These results suggest that specific immunomodulatory properties of probiotic bacteria should be characterized when developing clinical applications for extended target populations.

L30 ANSWER 7 OF 18 MEDLINE on STN DUPLICATE 2
2001393762. PubMed ID: 11228270. Oral carrageenan induces antigen-dependent **oral tolerance**: prevention of anaphylaxis and induction of lymphocyte anergy in a murine model of food **allergy**. Frossard C P; Hauser C; Eigenmann P A. (Department of Pediatrics, Division of Immunology and Allergy, University Hospital of Geneva, Switzerland.) Pediatric research, (2001 Mar) 49 (3) 417-22. Journal code: 0100714. ISSN: 0031-3998. Pub. country: United States. Language: English.

AB Immunosuppressive effects of carrageenan, a high-molecular-weight polysaccharide, on antibody and T cell responses have been previously demonstrated. However, its effect on anaphylaxis is unknown. Our objectives were to test carrageenan-mediated **oral tolerance** induction in young mice subsequently sensitized to a common cow's milk antigen. C3H/HeJ mice were fed or not lambda-carrageenan (0.5 g/L) and/or 0.01 mg/mL beta-lactoglobulin (BLG) for 5 d before oral sensitization with BLG and **cholera toxin**. Subsequently, the mice were challenged with BLG and symptom scores of anaphylaxis were recorded. Mesenteric lymph node cells, spleen cells, Peyer's patches cells, intraepithelial lymphocytes, and lamina propria lymphocytes were isolated and stimulated in vitro with BLG, IL-2, or left unstimulated. BLG-specific IgG, IgG(1), and IgG(2a) antibodies were measured. Pretreatment with carrageenan and BLG, but not pretreatment with either carrageenan or BLG alone or omission of pretreatment, diminished significantly the number of anaphylactic mice after BLG challenge (6.3 % versus 53 % in mice without pretreatment, p = 0.006). Mesenteric lymph nodes and spleen cells from pretreated mice proliferated less in presence of BLG or IL-2 than cells from sensitized control mice. Antigen-specific antibody production and passive cutaneous anaphylaxis was not suppressed by carrageenan and BLG pretreatment. In conclusion, carrageenan administered to young mice in conjunction with low doses of allergen before sensitization efficiently prevents anaphylaxis.

L30 ANSWER 8 OF 18 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 3
2002234136 EMBASE Suppression of specific and bystander IgE responses in a mouse model of oral sensitization to β-lactoglobulin. Von der Weid T.; Bulliard C.; Fritsche R.. Dr. T. Von der Weid, Department of Biosciences, Nestle Research Center, Nestec SA, PO Box 44, CH-1000 Lausanne 26, Switzerland. t.von-der-weid@rdls.nestle.com. International Archives of Allergy and Immunology 125/4 (307-315) 2001.
Refs: 27.
ISSN: 1018-2438. CODEN: IAAIEG. Pub. Country: Switzerland. Language: English. Summary Language: English.

AB Background: Mechanisms of systemic IgE suppression by **oral tolerance** have been extensively studied, but less is known about **oral tolerance** induction in mice challenged at mucosal sites. We have previously shown in systemically challenged mice that high-dose tolerance suppressed specific but not bystander IgE. In an attempt to mimic **oral tolerance** in food-allergic patients, we have investigated how IgE suppression could be induced in mice sensitized orally against β-lactoglobulin (BLG). Methods: Mice were immunized orally against BLG using **cholera toxin** as adjuvant. Before oral sensitization, mice were administered milk whey

proteins, either in the form of a single high-dose gavage, or by prolonged ad libitum administration of various doses. Results: Orally sensitized mice mounted a BLG-specific IgE response. In contrast to systemically challenged mice, a single high-dose gavage of whey protein given prior to the onset of oral sensitization resulted in the suppression of both specific and bystander IgE. When mice were fed moderate to low doses of milk whey proteins daily ad libitum in the drinking water during 3 weeks prior to oral sensitization, all doses effectively suppressed antigen-specific IgE. However, bystander IgE suppression was observed only at the lowest doses. When mice were tolerized during 4 days instead of 3 weeks, IgE titers remained unchanged. Conclusions: In orally sensitized mice, bystander IgE suppression depended on the dose of tolerogen, but also on its mode of administration. Mucosally induced IgE responses were suppressed by a mechanism that was distinct from that operating in the periphery. Copyright .COPYRGT. 2001 S. Karger AG, Basel.

L30 ANSWER 9 OF 18 MEDLINE on STN DUPLICATE 4
2000385105. PubMed ID: 10848926. Prolonged oral treatment with low doses of allergen conjugated to **cholera toxin** B subunit suppresses immunoglobulin E antibody responses in sensitized mice. Rask C; Holmgren J; Fredriksson M; Lindblad M; Nordstrom I; Sun J B; Czerkinsky C. (Department of Medical Microbiology and Immunology, Goteborg University, Goteborg, Sweden.) Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology, (2000 Jul) 30 (7) 1024-32. Journal code: 8906443. ISSN: 0954-7894. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: **Oral tolerance** is a long recognized method for inducing systemic immunological tolerance. However, large doses of antigen and frequent administrations are often required. By linking the antigen to the nontoxic mucosa-binding B subunit of **cholera toxin** (CTB), the required amount can be dramatically reduced. We have previously shown that mucosal administration of small amounts of antigens coupled to CTB can suppress peripheral Th1 cell-reactivity and associated inflammatory immunopathology in both naive and systemically-immunized animals. Induction of **oral tolerance** by repeated feeding of relatively small doses of antigen has, in some cases been shown to involve the generation of regulatory Th2-like CD4+ T cells, and hence could promote rather than suppress type I immunoglobulin (Ig) E-mediated allergic responses. OBJECTIVES: We examined whether oral prophylactic or therapeutic administration of a model allergen coupled to CTB would modulate allergen-specific IgE responses in high IgE responder Balb/c mice. METHODS: Ovalbumin (OVA) was used as a model allergen. Mice were treated perorally with free or CTB-coupled OVA before or after systemic priming with alum-adsorbed OVA. Allergen-specific IgE levels in serum were measured with the passive cutaneous anaphylaxis test at various time-points. RESULTS: Oral administration of a single low dose of CTB-linked OVA, prior to systemic sensitization and challenge with OVA, suppressed allergen-specific serum IgE antibody responses. Treatment with comparable doses of free OVA was much less effective. Most importantly, oral treatment with CTB-OVA conjugate could also suppress an already initiated IgE antibody response, but to achieve such a 'therapeutic effect', administration of multiple low doses of conjugate over a long time was required. Oral treatment with CTB-OVA conjugate could also effectively suppress antigen-specific Th1-mediated delayed-type hypersensitivity. Thus treatment with a CTB-conjugated model allergen can affect a broad range of T-cell-driven immune responses, even in antigen-experienced animals. CONCLUSION: These results may impact on the development of therapeutic vaccines against type I **allergies**.

L30 ANSWER 10 OF 18 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:580243 The Genuine Article (R) Number: 337ZH. A murine model of peanut anaphylaxis: T- and B-cell responses to a major peanut allergen mimic

human responses. Li X M (Reprint); Serebrisky D; Lee S Y; Huang C K; Bardina L; Schofield B H; Stanley J S; Burks A W; Bannon G A; Sampson H A. CUNY MT SINAI SCH MED, DEPT PEDIAT, 1 GUSTAVE L LEVY PL, NEW YORK, NY 10029 (Reprint); JOHNS HOPKINS UNIV, SCH HYG & PUBL HLTH, DEPT ENVIRONM HLTH SCI, BALTIMORE, MD; UNIV ARKANSAS, SCH MED, DEPT PEDIAT, LITTLE ROCK, AR 72204; UNIV ARKANSAS, SCH MED, DEPT BIOCHEM & MOL BIOL, LITTLE ROCK, AR 72204. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JUL 2000) Vol. 106, No. 1, Part 1, pp. 150-158. Publisher: MOSBY, INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Peanut **allergy** affects 0.6% of the US population. At the present time, allergen avoidance is the only therapeutic option. Animal models of Toed-induced anaphylaxis would Facilitate attempts to design novel immunotherapeutic strategies for the treatment of peanut **allergy**.

Objective: The purpose of this study was to develop a murine model of IgE-mediated peanut hypersensitivity that closely mimics human peanut **allergy**.

Methods: C3H/HeJ mice sensitized orally with freshly ground whole peanut and **cholera toxin** as adjuvant were challenged orally 3 and 5 weeks later with crude peanut extract. Anaphylactic reactions were determined. T- and B-cell responses to Ara h 1 and Ara h 2, the major peanut allergens, were characterized by evaluating splenocyte proliferative responses and IgE antibody concentrations. Furthermore, IgE antibodies in the sera of patients with peanut **allergy** and mice were compared for antibody binding to Ara h 2 isoforms and allergenic epitopes,

Results: Peanut-specific IgE was induced by oral peanut sensitization, and hypersensitivity reactions were provoked by feeding peanut to sensitized mice. The symptoms were similar to those seen in human subjects. Ara h 1- and Ara h 2-specific antibodies were present in the sera of mice with peanut **allergy**. Furthermore, these Ara h 2-specific IgE antibodies bound the same Ara h 2 isoforms and major allergenic epitopes as antibodies in the sera of human subjects with peanut **allergy**. Splenocytes from mice with peanut **allergy** exhibited proliferative responses to Ara h 1 and Ara h 2,

Conclusion: This murine model of peanut **allergy** mimics the clinical and immunologic characteristics of peanut **allergy** in human subjects and should be a useful tool for developing immunotherapeutic approaches for the treatment of peanut **allergy**
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L30 ANSWER 11 OF 18 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2000:221190 The Genuine Article (R) Number: 293KD. Suppression of specific IgE antibody responses by liposome-conjugated ovalbumin in mice sensitized with ovalbumin via the respiratory tract. Yoshikawa T; Uchida T; Naito S; Horino A; Taneichi M; Kato H; Komuro K; Nakano Y; Mori M; Nishinohara S; Chiba J; Kurata T; Tamura S (Reprint). NATL INST INFECT DIS, DEPT PATHOL, SHINJUKU KU, TOYAMA 1-23-1, TOKYO 1628640, JAPAN (Reprint); NATL INST INFECT DIS, DEPT PATHOL, SHINJUKU KU, TOKYO 1628640, JAPAN; NATL INST INFECT DIS, DEPT SAFETY RES BIOL, SHINJUKU KU, TOKYO 1628640, JAPAN; NOF CORP, TSUKUBA RES LAB, CHIBA, JAPAN; SCI UNIV TOKYO, IMMUNOL LAB, CHIBA, JAPAN. INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY (FEB 2000) Vol. 121, No. 2, pp. 108-115. Publisher: KARGER. ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND. ISSN: 1018-2438. Pub. country: JAPAN. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Previously we have shown that intranasal administration of ovalbumin (OVA) together with **cholera toxin** (CT) abrogates nasal tolerance to OVA, resulting in the induction of specific IgE antibody (Ab) responses, and that intraperitoneal injection of OVA coupled with liposomes (OVA-liposomes) induces a selective suppression of

IgE Ab responses to OVA. Whether OVA-liposomes suppress anti-OVA IgE Ab responses in mice sensitized with CT-combined OVA via the respiratory tract remains to be clarified. Methods: In some experiments, mice were given OVA, liposomes or OVA-liposomes with or without CT intranasally three times, at 2-week intervals (weeks 0, 2 and 4). In other experiments, mice were given OVA-liposomes intranasally 2 days before or 1 and 3 weeks after CT-combined OVA (week 0), which was administered intranasally three times, at 2-week intervals (weeks 0, 2 and 4). Two weeks after the third administration of CT-combined OVA (week 0), nasal wash and serum IgA, IgG and IgE Ab responses were assayed. Results: Pretreatment: with OVA-liposomes suppressed IgE Ab responses to CT-combined OVA, with a significantly high production of: both nasal IgA and serum IgG Absolute Moreover, treatment with OVA-liposomes 1 and 3 weeks after CT-combined OVA administration also suppressed IgE Ab responses. The suppression of anti-OVA IgE Ab production by OVA-liposomes was accompanied by a simultaneous enhancement of specific IgA and IgG (IgG1, and especially IgG2a) Ab production. Conclusions: Postimmunization treatment with OVA-liposomes, as well as preimmunization treatment, suppressed specific IgE Ab responses in mice sensitized intranasally with CT-combined OVA. Allergens conjugated to liposomes may be appropriate for preventing the development of **allergies** to inhaled or dietary antigens in humans. Copyright (C) 2000 S. Karger AG, Basel.

L30 ANSWER 12 OF 18 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:157502 The Genuine Article (R) Number: 167JW. A murine model of IgE-mediated cow's milk hypersensitivity. Li X M (Reprint); Schofield B H; Huang C K; Kleiner G I; Sampson H A. CUNY MT SINAI SCH MED, DEPT PEDIAT, BOX 1198, 1 GUSTAVE L LEVY PL, NEW YORK, NY 10029 (Reprint); JOHNS HOPKINS UNIV, SCH HYG & PUBL HLTH, DEPT ENVIRONM HLTH SCI, BALTIMORE, MD. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (FEB 1999) Vol. 103, No. 2, Part 1, pp. 206-214. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: USA . Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Cow's milk **allergy** (CMA) is one of the leading causes of food **allergy** in children. Understanding the mechanisms involved in the development of CMA has been hampered by the lack of suitable animal models.

Objective: We sought to develop a mouse model of IgE-mediated cow's milk hypersensitivity (CMH) that mimics the clinical features of immediate CMA in humans.

Methods: Three-week-old C3H/HeJ mice were sensitized by intragastric administration of cow's milk (CM) plus **cholera toxin** and boosted 5 times at weekly intervals.

Results: Chi-specific IgE antibody levels were significantly increased at 3 weeks and peaked at 6 weeks after the initial feeding, Intragastric challenge with Chi at week 6 elicited systemic anaphylaxis accompanied by vascular leakage, significantly increased plasma histamine, and increased intestinal permeability to casein, Histologic examination of intestinal tissue revealed marked vascular congestion, edema, and sloughing of enterocytes. The role of IgE in mediating CMH was confirmed by abrogation of passive cutaneous anaphylaxis reactions by heat inactivation of immune sera. Development of IgE-mediated CMH in this model is likely to be T-H2 cell mediated because in vitro stimulation of spleen cells from mice allergic to CM induced significant increases in the levels of IL-4 and IL-5, but not IFN-gamma.

Conclusion: This model should provide a useful tool for evaluating the immunopathogenic mechanisms involved in CMA and for exploring new therapeutic approaches.

L30 ANSWER 13 OF 18 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:367268 The Genuine Article (R) Number: 193LE. Modulation of an allergic immune response via the mucosal route in a murine model of inhalative

type-I **allergy**. Wiedermann U (Reprint); JahnSchmid B; Repa A; Kraft D; Ebner C. UNIV VIENNA, AKH, INST GEN & EXPT PATHOL, DIV IMMUNOPATHOL, WAEHRINGER GUERTEL 18-20, A-1090 VIENNA, AUSTRIA (Reprint). INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY (FEB-APR 1999) Vol. 118, No. 2-4, pp. 129-132. Publisher: KARGER. ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND. ISSN: 1018-2438. Pub. country: AUSTRIA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A murine model of aerosol inhalation, leading to sensitization to birch pollen (BP) and its major allergen Bet v 1, was established in order to try to influence type-1 allergic immune responses via the mucosal route. We previously demonstrated that simultaneous inhalation of BP and **cholera toxin**, a potent mucosal adjuvant, induced a Th1-like immune response to the allergen in naive mice and modulated allergic immune responses in sensitized mice. In contrast to cholera holotoxin, mucosal application of the cholera B subunit (CTB) conjugated to antigen has been shown to induce peripheral tolerance in certain models of Th1-based autoimmune diseases. In the present study we investigated the potential of such an antigen delivery system to suppress Th2-based, allergic immune responses. Mucosal administration of CTB/Bet v 1 conjugates prior to sensitization led to significantly increased allergen-specific IgE/IgG1 and IgG2a antibody levels and cytokine production (IL-5, IFN-gamma) in vitro. Thus, CTB coupled to Bet v 1 acted as an adjuvant rather than a tolerogen. On the other hand we noted that mucosal application of CTB coupled to ovalbumin led to marked suppression of antigen-specific IgE antibody levels and IL-5 production in vitro and thereby restricted allergic sensitization. These results indicated that the effects of CTB/antigen conjugates depended on the nature of the antigen. In contrast to Bet v 1 coupled to CTB, nasal as well as oral application of low doses of unconjugated, Bet v 1 prior to aerosol sensitization inhibited allergen-specific antibody responses of all isotypes, cutaneous type-1 skin tests in vivo as well as allergen-specific lymphoproliferative responses and cytokine production (IL-4, IL-5, IL-10, IFN-gamma) in vitro, suggesting that both T- and B-cell tolerance to the allergen were induced. Taken together, mucosal tolerance induction as well as the use of certain transmucosal antigen delivery systems might be promising new strategies to modulate type-1 allergic immune responses.

L30 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN

1999:52433 Document No. 130:250778 **Oral tolerance** and anti-pathological vaccines. Czerkinsky, C.; Sun, J.-B.; Holmgren, J. (INSERM Unit 364, Cellular and Molecular Immunology, Faculte de Medecine-Pasteur, Nice, 06107, Fr.). Current Topics in Microbiology and Immunology, 236(Defense of Mucosal Surfaces: Pathogenesis, Immunity and Vaccines), 79-91 (English) 1999. CODEN: CTMIA3. ISSN: 0070-217X. Publisher: Springer-Verlag.

AB A review with 50 refs. Topics discussed include mechanism of induction and expression of peripheral tolerance after mucosal delivery of antigens; mucosal immunotherapy; **cholera toxin** B subunit as a mucosal carrier-immunomodulating system for anti-pathol. vaccination; treatment of organ-specific autoimmune diseases; prevention of graft rejection and type I **allergies**; and mucosal vaccines for simultaneous induction of anti-infectious and anti-pathol. immunity.

L30 ANSWER 15 OF 18 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 5

1999014346 EMBASE Oral administration of a dominant T-cell determinant peptide inhibits allergen-specific T(H1) and T(H2) cell responses in Cry j 2-primed mice. Hirahara K.; Saito S.; Serizawa N.; Sasaki R.; Sakaguchi M.; Inouye S.; Taniguchi Y.; Kaminogawa S.; Shiraishi A.. Dr. A. Shiraishi, Biological Research Laboratories, Sankyo Co, Ltd, 2-58 Hiromachi 1-chome, Shinagawa-ku, Tokyo 140-8710, Japan. Journal of Allergy and Clinical Immunology 102/6 I (961-967) 1998.

Refs: 36.
ISSN: 0091-6749. CODEN: JACIBY. Pub. Country: United States. Language: English. Summary Language: English.

AB Background: Oral immunotherapy with a peptide for allergic immune responses is theoretically a promising therapy but has not been established yet. Objective: To evaluate immune suppressive efficacy of oral administration of an immunodominant peptide, we investigated changes in T- cell proliferation, T(H1)- and T(H2)-cytokine production, and T(H1)- and T(H2)-mediated antibody production in mice after oral administration of a peptide. Methods: Peptide p246-259, containing a dominant T-cell determinant of Cry j 2, which is the major allergen in Japanese cedar pollen, was used in this study. Groups of mice received p246-259 or PBS alone before or after they were primed intranasally with Cry j 2 and **cholera toxin**. In another experiment mice were primed intraperitoneally with Cry j 2 and alum. Proliferative response and cytokine production by nasal-associated lymph node cells against Cry j 2 were investigated. Amounts of systemic anti-Cry j 2 IgE and IgG antibodies were also measured. Results: Oral administration of the peptide to mice before, or even after, the sensitization induced **oral tolerance** in T-cell responses against the allergen; the tolerance was associated with decreased production of T(H1) (IFN-γ and IL-2) and T(H2) (IL-4) cytokines. Allergen-specific T(H1)-mediated (IgG2a and IgG2b) and T(H2)-mediated (IgG1 and IgE) antibody responses were also inhibited. Conclusions: Oral administration of a dominant T-cell determinant peptide induces immunologic tolerance in both T(H1) and T(H2) cell responses against the whole protein allergen. Our study is the first, to our knowledge, to demonstrate the potential for peptide-based oral immunotherapy in order to treat allergic immune responses.

L30 ANSWER 16 OF 18 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1998:828125 The Genuine Article (R) Number: 131TN. The hygiene hypothesis revised: is the rising frequency of **allergy** due to changes in the intestinal flora?. Wold A E (Reprint). GULDHEDSGATAN 10, S-41346 GOTHENBURG, SWEDEN (Reprint); GOTHENBURG UNIV, DEPT CLIN IMMUNOL, GOTHENBURG, SWEDEN. ALLERGY (AUG 1998) Vol. 53, Supp. [46], pp. 20-25. Publisher: MUNKSGAARD INT PUBL LTD. 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK. ISSN: 0105-4538. Pub. country: SWEDEN. Language: English.

L30 ANSWER 17 OF 18 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1998:61916 The Genuine Article (R) Number: YQ647. Murine model of IgE production with a predominant Th2-response by feeding protein antigen without adjuvants. Ito K; InagakiOhara K; Murosaki S; Nishimura H; Shimokata T; Torii S; Matsuda T; Yoshikai Y (Reprint). NAGOYA UNIV, SCH MED, DIS MECHANISM & CONTROL RES INST, LAB HOST DEF & GERMFREE LIFE, SHOWA KU, NAGOYA, AICHI 466, JAPAN (Reprint); NAGOYA UNIV, SCH MED, DIS MECHANISM & CONTROL RES INST, LAB HOST DEF & GERMFREE LIFE, SHOWA KU, NAGOYA, AICHI 466, JAPAN; NAGOYA UNIV, SCH MED, DEPT PEDIAT, SHOWA KU, NAGOYA, AICHI 466, JAPAN; NAGOYA UNIV, SCH AGR SCI, DEPT APPL BIOL SCI, NAGOYA, AICHI, JAPAN; TAKEDA FOOD PROD LTD, DEPT DEV, ITAMI, HYOGO, JAPAN. EUROPEAN JOURNAL OF IMMUNOLOGY (DEC 1997) Vol. 27, No. 12, pp. 3427-3437. Publisher: VCH PUBLISHERS INC. 303 NW 12TH AVE, DEERFIELD BEACH, FL 33442-1788. ISSN: 0014-2980. Pub. country: JAPAN. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Stimulation of systemic antigen-specific IgE production plays an important role in the mediation of food **allergy**; however, the mechanism of IgE production against food antigens is not fully understood. The development of relevant animal models may help to elucidate the pathogenesis of food **allergy**. We here show that DBA/2 mice receiving a casein diet without any adjuvant produced high levels of IgE specific for casein, accompanied by predominant Th2-like responses in liver lymphocytes, mesenteric lymph node cells and spleen cells. This model of IgE production produced by feeding protein antigen as a

constituent of the diet can be applied to investigate the mechanism of IgE production and to develop reagents for controlling food **allergy**.

L30 ANSWER 18 OF 18 MEDLINE on STN
93050830. PubMed ID: 1426671. Oral administration of immunomodulators and the mucosal immune system. Revillard J P; Cozon G; Czerkinsky C. (Laboratoire d'Immunologie, INSERM U80 CNRS URA 1177 UCBL, Hopital E. Herriot, Lyon, France.) Developments in biological standardization, (1992) 77 31-7. Ref: 25. Journal code: 0427140. ISSN: 0301-5149. Pub. country: Switzerland. Language: English.
AB Orally administered antigens reach the lymphoid tissue in Peyer's patches in the gut where they initiate an immune response with clonal expansion of antigen-specific T and B cells. Activated T cells migrate through lymph and blood to intestinal epithelium (intra-epithelial leukocytes) whereas activated B cells migrate to the lamina propria, other mucosae and exocrine glands where they differentiate into plasma cells secreting polymeric IgA1 or IgA2. These antibodies are transported across the epithelial cells after binding to a poly-Ig receptor, then excreted in the lumen as secretory IgA. Reciprocal interactions have been demonstrated between lymphoid and epithelial cells in the mucosae. Oral administration of antigens in different experimental models may induce the production of secretory antibodies and/or systemic unresponsiveness with suppression of delayed-type hypersensitivity or specific IgG and IgE antibody production or both. New strategies are currently being explored for the development of oral vaccines using recombinant antigens or viral vectors (e.g. pox-viruses, vaccinia virus, **cholera toxin** B subunit etc.). Conversely, immunomodulating compounds or procedures which could enhance specific **oral tolerance** in association with antigen would have considerable therapeutic applications in auto-immune diseases and **allergy**.

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L31 2 L26 AND ENTEROTOXIN

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L32 ANSWER 1 OF 2 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2003192785 EMBASE Mucosal adjuvants and anti-infection and anti-immunopathology vaccines based on cholera toxin, cholera toxin B subunit and CpG DNA. Holmgren J.; Harandi A.M.; Czerkinsky C.. J. Holmgren, Department of Medical Microbiology, Goteborg Univ. Vacc. Res. Institute, Goteborg University, Guldhedsgatan 10A, SE-413 46 Goteborg, Sweden. jan.holmgren@microbio.gu.se. Expert Review of Vaccines 2/2 (205-217) 2003.
Refs: 64.
ISSN: 1476-0584. CODEN: ERVXAX. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB The mucosal immune system consists of an integrated network of lymphoid cells that work in concert with innate host factors to promote host defence. Mucosal immunization can be used both to protect the mucosal surfaces against colonization and invasion by microbial pathogens and to provide a means for immunological treatment of selected autoimmune, allergic or infectious-immunopathological disorders through the induction of antigen-specific tolerance. The development of mucosal vaccines, whether for prevention of infectious diseases or for **oral tolerance** immunotherapy, requires efficient antigen delivery and adjuvant systems. Significant progress has recently been made to generate

partly or wholly detoxified derivatives of cholera toxin (including the completely nontoxic cholera toxin B subunit) and the closely related Escherichia coli heat-labile **enterotoxin**, with retained adjuvant activity. Cholera toxin B subunit is a protective component of a widely registered oral vaccine against cholera, and has proven to be a promising vector for either giving rise to anti-infective immunity or for inducing peripheral anti-inflammatory tolerance to chemically or genetically linked foreign antigens administered mucosally. Promising advances have also recently been made In the design of efficient mucosal adjuvants based on bacterial DNA that contains CpG-motifs and various imidazoquinoline compounds binding to different Toll-like receptors on mucosal antigen-presenting cells.

L32 ANSWER 2 OF 2 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:550226 The Genuine Article (R) Number: 334CP. Prolonged oral treatment with low doses of allergen conjugated to cholera toxin B subunit suppresses immunoglobulin E antibody responses in sensitized mice. Rask C; Holmgren J (Reprint); Fredriksson M; Lindblad M; Nordstrom I; Sun J B; Czerkinsky C. GOTHENBURG UNIV, DEPT MED MICROBIOL & IMMUNOL, GULDHEDSGATAN 10, S-41346 GOTHENBURG, SWEDEN (Reprint); GOTHENBURG UNIV, DEPT MED MICROBIOL & IMMUNOL, S-41346 GOTHENBURG, SWEDEN; FAC MED PASTEUR, INSERM, U364, NICE, FRANCE. CLINICAL AND EXPERIMENTAL ALLERGY (JUL 2000) Vol. 30, No. 7, pp. 1024-1032. Publisher: BLACKWELL SCIENCE LTD. P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND. ISSN: 0954-7894. Pub. country: SWEDEN; FRANCE. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background **Oral tolerance** is a long recognized method for inducing systemic immunological tolerance. However, large doses of antigen and frequent administrations are often required. By linking the antigen to the nontoxic mucosa-binding B subunit of cholera toxin (CTB), the required amount can be dramatically reduced. We have previously shown that mucosal administration of small amounts of antigens coupled to CTB can suppress peripheral Th1 cell-reactivity and associated inflammatory immunopathology in both naive and systemically-immunized animals. Induction of **oral tolerance** by repeated feeding of relatively small doses of antigen has, in some cases been shown to involve the generation of regulatory Th2-like CD4(+) T cells, and hence could promote rather than suppress type I immunoglobulin (Ig) E-mediated allergic responses.

Objectives We examined whether oral prophylactic or therapeutic administration of a model allergen coupled to CTB would modulate allergen-specific IgE responses in high IgE responder Balb/c mice.

Methods Ovalbumin (OVA) was used as a model allergen. Mice were treated perorally with free or CTB-coupled OVA before or after systemic priming with alum-adsorbed OVA. Allergen-specific IgE levels in serum were measured with the passive cutaneous anaphylaxis test at various time-points.

Results Oral administration of a single low dose of CTB-linked OVA, prior to systemic sensitization and challenge with OVA, suppressed allergen-specific serum IgE antibody responses. Treatment with comparable doses of free OVA was much less effective. Most importantly, oral treatment with CTB-OVA conjugate could also suppress an already initiated IgE antibody response, but to achieve such a 'therapeutic effect', administration of multiple low doses of conjugate over a long time was required. Oral treatment with CTB-OVA conjugate could also effectively suppress antigen-specific Th1-mediated delayed-type hypersensitivity. Thus treatment with a CTB-conjugated model allergen can affect a broad range of T-cell-driven immune responses, even in antigen-experienced animals.

Conclusion These results may impact on the development of therapeutic vaccines against type I **allergies**.

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L34 361 DUP REMOVE L26 (253 DUPLICATES REMOVED)

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L36 42 DUP REMOVE L35 (0 DUPLICATES REMOVED)

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L36 ANSWER 1 OF 42 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
2003357899 EMBASE Gastric Helicobacter infection inhibits development of **oral tolerance** to food antigens in mice. Matysiak-Budnik T.; Van Niel G.; Megraud F.; Mayo K.; Bevilacqua C.; Gaboriau-Routhiau V.; Moreau M.-C.; Heyman M.. T. Matysiak-Budnik, INSERM EMI-0212, Fac. de Med. Necker-Enfants Malades, 156 rue de Vaugirard, 75730 Paris, France. matysiak@necker.fr. Infection and Immunity 71/9 (5219-5224) 1 Sep 2003. Refs: 39.
ISSN: 0019-9567. CODEN: INFIBR. Pub. Country: United States. Language: English. Summary Language: English.

AB The increase in the transcellular passage of intact antigens across the digestive epithelium infected with Helicobacterpylori may interfere with the regulation of mucosal immune responses. The aim of this work was to study the capacity of Helicobacter infection to inhibit the development of **oral tolerance** or to promote allergic sensitization and the capacity of a gastro-protective agent, rebamipide, to interfere with these processes in mice. **Oral tolerance** to ovalbumin (**OVA**) was studied in 48 C3H/He 4-week-old mice divided into four groups: (i) **OVA**-sensitized mice; (ii) **OVA**-"tolerized" mice (that is, mice that were rendered immunologically tolerant); (iii) H. felis-infected, **OVA**-tolerized mice; (iv) and H. felis-infected, **OVA**-tolerized, rebamipide-treated mice. Oral sensitization to hen egg lysozyme (HEL) was studied in 48 mice divided mice divided into four groups: (i) controls; (ii) HEL-sensitized mice; (iii) H. felis-infected, HEL-sensitized mice; and (iv) H. felis-infected, HEL-sensitized, rebamipide-treated mice. Specific anti-**OVA** or anti-HEL immunoglobulin E (IgE) and IgG1/IgG2a serum titers were measured by enzyme-linked immunosorbent assay. Additionally, the capacity of rebamipide to interfere with antigen presentation and T-cell activation in vitro, as well as absorption of rebamipide across the epithelial monolayer, was tested. H. felis infection led to the inhibition of **oral tolerance** to **OVA**, but rebamipide prevented this inhibitive effect of H. felis. H. felis infection did not enhance the sensitization to HEL, but rebamipide inhibited the development of this sensitization. Moreover, rebamipide inhibited in a dose-dependent manner antigen presentation and T-cell activation in vitro and was shown to be able to cross the epithelium at a concentration capable of inducing this inhibitory effect. We conclude that H. felis can inhibit the development of **oral tolerance** to **OVA** in mice and that this inhibition is prevented by rebamipide.

L36 ANSWER 2 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:978085 The Genuine Article (R) Number: 738LA. The [173-196] fragment of ovalbumin suppresses ovalbumin-specific rat IgE responses. Ben Nasser I; Boyaka P N; Ben Aissa F F; Jeddi M; Tome D (Reprint). INRA, INA PG, Unite 914 Physiol Nutr & Comportement Almentaire, 16, Rue Claude Bernard, F-75231 Paris 05, France (Reprint); INRA, INA PG, Unite 914 Physiol Nutr &

Comportement Almentaire, F-75231 Paris 05, France; Fac Pharm Monastir, Microbiol Lab, Monastir, Tunisia; Univ Alabama, Dept Microbiol, Birmingham, AL USA; Univ Alabama, Immunobiol Vaccine Ctr, Birmingham, AL USA; Fac Med, Lab Hematol, Tunis, Tunisia. INTERNATIONAL IMMUNOPHARMACOLOGY (NOV 2003) Vol. 3, No. 12, pp. 1569-1579. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 1567-5769. Pub. country: France; Tunisia; USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Peptides and protein hydrolysates are attractive tools for the induction of tolerance or regulation of targeted B and/or T cell responses. In vivo, peptides are mainly produced by the action of digestive enzymes or following the processing of exogenous antigens by antigen-presenting cells (APCs). In vitro, these molecules are generally produced by enzymatic digestion and chemical hydrolysis of proteins. We investigated the T and B cell determinants of the major food allergen ovalbumin (nOVA) in rat by analyzing (1) the stimulatory effect of nOVA peptides generated by cyanogen bromide (CNBr) cleavage on nOVA-specific T cells, and (2) the potential of CNBr-derived **OVA** fractions to induce **oral tolerance** to nOVA. Peptide fractions of the CNBr-hydrolysated **OVA** were isolated by high-pressure liquid chromatography and tested for their ability to stimulate nOVA-specific T cells isolated from rats parenterally immunized with nOVA. The nOVA fractions containing the stimulatory determinants were then intragastrically administered to rat to test their potential to induce **oral tolerance**. The hole CNBr hydolysate stimulated proliferation of nOVA-specific T cells. Three out of the five HPLC-purified peptidic fractions were also able to stimulate proliferation and cytokine production by nOVA-specific T cells. A peptide fraction exhibiting a single peak by HPLC contained the 173-196 nOVA segment and stimulated nOVA-specific T cells. This segment also promoted **oral tolerance** to nOVA and reduced IgE responses. CNBr hydrolysis releases several peptides with stimulatory effect on nOVA-specific T cells including a new nOVA [173-196] T cell determinant which induces **oral tolerance** to nOVA. (C) 2003 Elsevier B.V. All rights reserved.

L36 ANSWER 3 OF 42 MEDLINE on STN

2003221489. PubMed ID: 12743572. Oral administration of specific antigens to **allergy**-prone infant dogs induces IL-10 and TGF-beta expression and prevents **allergy** in adult life. Zemann Barbara; Schwaerzler Christoph; Griot-Wenk Monika; Nefzger Marijke; Mayer Peter; Schneider Heinz; de Weck Alain; Carballido Jose M; Liehl Ekke. (Novartis Research Institute, Vienna, Austria.) Journal of allergy and clinical immunology, (2003 May) 111 (5) 1069-75. Journal code: 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Oral administration of allergens can induce immune tolerance to specific allergens in rodents and hence might be a possibility to prevent and treat allergic diseases in human subjects. However, the gastrointestinal tract of mice is different from that of human subjects. The absorption of specific antigens and subsequent antigen presentation to intestinal T cells is different in both species, making it difficult to extrapolate results. OBJECTIVE: We investigated primary **oral tolerance** to ovalbumin (**OVA**) in an IgE high-responder dog model, which is more predictive for human allergic diseases than corresponding rodent models. METHODS: **Oral tolerance** was induced by means of a 28-day treatment with **OVA** dissolved in cow's milk. RESULTS: We observed reduced **OVA**-specific IgE and IgG production in response to ensuing subcutaneous challenges. Allergic conjunctivitis induced by means of ocular and airway provocation was significantly reduced in tolerized animals compared with that seen in nontolerized control animals. In addition, eosinophilia and neutrophilia in bronchoalveolar lavage fluid and bronchoconstriction after airway allergen challenge were significantly suppressed in tolerized animals.

Cytokine analysis by means of real-time PCR on bronchoalveloar fluid cells after allergen challenge revealed a high-level expression of IL-10 and transforming growth factor beta, predominantly in the CD14(+) population. CONCLUSION: Feeding infant beagles with **OVA** for 4 weeks is sufficient to prevent hallmark manifestations of asthma and **allergy** in adult life. The mechanism of **oral tolerance** involved an increased expression of IL-10 and transforming growth factor beta cytokines.

L36 ANSWER 4 OF 42 MEDLINE on STN

2003392185. PubMed ID: 12911780. Epicutaneous exposure to protein antigen and food **allergy**. Hsieh K-Y; Tsai C-C; Wu C H Herbert; Lin R-H. (Graduate Institute of Immunology, College of Medicine, National Taiwan University, Taipei, Taiwan.) Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology, (2003 Aug) 33 (8) 1067-75. Journal code: 8906443. ISSN: 0954-7894. Pub. country: England: United Kingdom. Language: English.

AB BACKGROUND: The aetiology of food **allergy** remains unclear. Although failure to develop or breakdown in **oral tolerance** has been proposed, the existence of physiologic sensitization routes other than the gastrointestinal tract cannot be excluded. OBJECTIVE: The purpose of this study is to clarify whether or not exposure to allergen through the skin can promote food **allergy**. METHODS: BALB/c mice were shaved on the back, and a patch impregnated with 100 micro g of ovalbumin (**OVA**) was applied to the dorsal skin for a 1-week period and then removed. After three courses of sensitization, **OVA**-specific antibodies in sera were measured, and then mice were orally challenged with 50 mg of **OVA**. Anaphylactic symptoms, plasma histamine levels, and histology of intestines and lungs after oral challenge were examined. RESULTS: Epicutaneous (EC) sensitization of mice to **OVA** induced a high level of **OVA**-specific IgE. Subsequent oral challenge with **OVA** resulted in symptoms of systemic anaphylaxis with elevated levels of plasma histamine as well as histological changes in both intestines and lungs. In the presence of anti-IL-4 antibodies, EC sensitization failed to provoke an IgE response, but still induced a Th2-predominant cellular immune response in lungs after oral challenge. CONCLUSION: We demonstrated for the first time that food **allergy** can be induced by allergen exposure through the skin. Our results identify a novel role of EC sensitization in the pathogenesis of food **allergy**.

L36 ANSWER 5 OF 42 MEDLINE on STN

2003154831. PubMed ID: 12671056. Characterization of lymphocyte responses to peanuts in normal children, peanut-allergic children, and allergic children who acquired tolerance to peanuts. Turcanu Victor; Maleki Soheila J; Lack Gideon. (Department of Paediatrics, Imperial College Faculty of Medicine, London, United Kingdom.) Journal of clinical investigation, (2003 Apr) 111 (7) 1065-72. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB Comparing lymphocyte responses to allergenic and nonallergenic foods could reveal the differences between pathogenic and normal immune responses to foods. Defining the cytokine-producing phenotypes of peanut-specific lymphocytes from peanut-allergic children, children who outgrew peanut **allergy**, and children who have always tolerated peanuts may be useful for understanding the mechanisms of food tolerance. Investigating immune responses against foods is hindered, however, by the fact that circulating food antigen-specific lymphocytes are very rare. In a novel approach we used carboxyfluorescein succinimidyl ester to detect peanut-specific lymphocytes by flow cytometry. We confirmed that these cells are indeed peanut specific by cloning. Peanut-allergic donors show Th2 polarization of cytokine production by peanut-specific cells (IFN-gamma (low), TNF-alpha (low), IL-4 (high), IL-5 (high), IL-13

(high)). Conversely, nonallergic children and children who have outgrown their **allergy** show Th1 skewing to peanut antigens (IFN-gamma(high), TNF-alpha (high), IL-4 (low), IL-5 (low), IL-13(low)), similarly to nonallergenic food antigens (beta-lactoglobulin, **OVA**). This finding suggests that peanut antigens do not intrinsically induce Th2 skewing, but that the type of response depends upon the donor's allergic status. In conclusion, food allergic status is characterized by a Th2 response whereas Th1-skewed responses underlie **oral tolerance**.

L36 ANSWER 6 OF 42 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2003088470 EMBASE Suppression of allergic reaction by λ-carrageenan: Toll-like receptor 4/MyD88-dependent and -independent modulation of immunity. Tsuji R.F.; Hoshino K.; Noro Y.; Tsuji N.M.; Kurokawa T.; Masuda T.; Akira S.; Nowak B.. R.F. Tsuji, Noda Inst. for Scientific Research, 399 Noda, Nod-shi, Chiba-ken 278-0037, Japan. tsujir@Xa2.so-net.ne.jp. Clinical and Experimental Allergy 33/2 (249-258) 2003.
Refs: 41.
ISSN: 0954-7894. CODEN: CLEAEN. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Background: Recognition of foreign substances by innate immunity through pattern recognition receptors (PRRs) regulates acquired immunity such as allergic reaction. Because PRRs recognize heterogeneous ligands, daily food intake can potentially regulate immune allergic reaction. Objective: Elucidation of the effect of λ-carrageenan on allergic reactions was aimed. Method: IFN-γ and IL-4 was measured in in vitro T cell-stimulated culture. Cytokine production from macrophages in response to λ-carrageenan was measured as indicator for innate immunity activation. Mice were immunized with **OVA** in alum to induce specific IgE, and then histamine release was induced by systemic injection of **OVA**. Results: Activation of innate immunity by λ-carrageenan is dependent on Toll-like receptor-4 (TLR4) and MyD88, in which induction of pro-inflammatory cytokines such as TNF-α and IL-6 was largely impaired in macrophages from TLR4- and MyD88-deficient mice. Footpad oedema, a model for in vivo inflammatory reactions, was significantly reduced in these mice. Similar to recent evidence showing a preference for the stimulation of Th1 via TLR/MyD88 signalling, λ-carrageenan showed enhanced IFN-γ and decreased IL-4 in stimulated T cell cultures. Interestingly, increased IFN-γ production was still seen in TLR4- and MyD88-deficient splenocytes. Oral administration of λ-carrageenan to immunized mice successfully decreased **OVA**-specific IgE, and λ-carrageenan was also effective in previously immunized mice. Further, serum histamine release upon systemic challenge of **OVA** was significantly inhibited. Neither **OVA**-specific IgG1/IgG2a nor cytokine secretion from in vitro cultures were altered, suggesting the involvement of multiple PRRs as demonstrated by TLR4/MyD88-independent IFN-γ up-regulation. The simultaneous feeding of **OVA** with lipopolysaccharide abrogated **oral tolerance**, but λ-carrageenan was not only devoid of such an effect but was also found to promote **oral tolerance** in the absence of TLR4. Conclusion: λ-Carrageenan was suggested to be a useful dietary supplement to ameliorate allergic reactions while maintaining **oral tolerance**-dependent intestinal homeostasis.

L36 ANSWER 7 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

2003:37332 Document No. 138:220714 Zinc deficiency suppresses the development of **oral tolerance** in rats. Finamore, Alberto; Roselli, Marianna; Merendino, Nicolo; Nobili, Fabio; Vignolini, Francesco; Mengheri, Elena (Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione, Rome, 00178, Italy). Journal of Nutrition, 133(1), 191-198 (English) 2003. CODEN: JONUAI. ISSN: 0022-3166. Publisher:

American Society for Nutritional Sciences.

AB **Oral tolerance** is a specific immune unresponsiveness to food antigens to prevent hypersensitivity reactions. We investigated whether Zn deficiency affects **oral tolerance.** Rats were fed a control (C) or Zn-deficient (ZD) diet, or pair-fed (PF) to ZD rats for 28 d. Beginning on d 7, rats were administered ovalbumin (**OVA**) orally to induce tolerance, or PBS 3 times/wk, and were then immunized by **OVA** injection. The proliferation of mesenteric lymph node (MLN) and spleen lymphocytes after in vitro **OVA** stimulation and the delayed-type hypersensitivity were higher in **OVA**-fed ZD than in **OVA**-fed C rats and not different between **OVA**- and PBS-fed ZD rats, indicating a suppression of tolerance. Lymphocyte proliferation did not differ between PF and C rats. Expressions of cytokines involved in **oral tolerance,** i.e., interleukin (IL)-4, IL-10 and transforming growth factor-β, were higher in **OVA**- than in PBS-fed C rats, but not in ZD rats. Apoptosis was higher in **OVA**- than in PBS-fed C rats but not different between **OVA**- and PBS-fed ZD rats. Inflammation and ulcerations that were not present in ZD rats on d 7 (ZD7) developed in **OVA**- or PBS-fed ZD rats. Compared with ZD7 rats, tumor necrosis factor-α and cytokine-induced neutrophil chemoattractant were higher in **OVA**- and PBS-fed ZD rats, whereas interferon-γ increased only in **OVA**-fed ZD rats. In conclusion, Zn deficiency suppresses **oral tolerance** through dysregulation of cytokine expression and lack of antigen-specific clonal deletion. We suggest that abrogation of tolerance may lead to development of mucosal inflammation and damage.

L36 ANSWER 8 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

2003:216601 Document No. 138:352681 Lack of **oral tolerance** in aging is due to sequential loss of Peyer's patch cell interactions. Kato, Hirotomo; Fujihashi, Kohtaro; Kato, Rie; Dohi, Taeko; Fujihashi, Keiko; Hagiwara, Yukari; Kataoka, Kosuke; Kobayashi, Ryoki; McGhee, Jerry R. (Immunobiology Vaccine Center, Departments of Microbiology and Oral Biology, University of Alabama at Birmingham, Birmingham, AL, 35294-2170, USA). International Immunology, 15(2), 145-158 (English) 2003. CODEN: INIMEN. ISSN: 0953-8178. Publisher: Oxford University Press.

AB Our past studies showed that Peyer's patches were required for the induction of **oral tolerance** to the protein antigen ovalbumin (**OVA**), but not to the hapten 2,4,6-trinitrobenzene sulfonic acid (TNBS). In the present study, the effects of immunosenescence on **oral tolerance** induction were assessed with these two toleragens. Significant redns. in **OVA** -specific serum IgG antibody and CD4+ T cell responses to subsequent challenge were observed in **OVA**-fed, young adult mice. Importantly, these reduced anti-**OVA** antibody responses were associated with delayed-type hypersensitivity, and antigen-induced CD4+ Th1- and Th2-type cytokine responses. On the other hand, aged mice fed **OVA** failed to develop **oral tolerance.** Thus, CD4+ T cells from Peyer's patches produced selected Th2- but no Th1-type cytokines. The TNP-specific serum IgG antibody and T cell responses were significantly diminished by prior TNBS feeding in young adult, 6- to 8-mo-old and 12- to 14-mo-old, but not in senescent, 2-yr-old mice. Finally, we have directly assessed dendritic cell subsets and T cell responses in Peyer's patches, and their function in tolerance induction was impaired at an earlier stage of life. These results suggest that lack of **oral tolerance** to the protein **OVA** during aging is the result of dysfunctional Peyer's patches.

L36 ANSWER 9 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2003:477629 The Genuine Article (R) Number: 684LN. Further evidence regarding the effect of dietary protein on **oral tolerance** against beta-lactoglobulin through Th1-mediated immune response in mice.

Ahmed S; Satter M A; Yamamoto S; Maeda K; Minato Y; Ota F (Reprint). Univ Tokushima, Dept Food Microbiol, Tokushima 7708503, Japan (Reprint); Univ Tokushima, Hlth Serv Ctr, Tokushima 7708503, Japan; Univ Tokushima, Fac Med, Sch Nutr, Dept Appl Nutr, Tokushima 7708503, Japan. JOURNAL OF NUTRITIONAL SCIENCE AND VITAMINOLOGY (APR 2003) Vol. 49, No. 2, pp. 112-119. Publisher: CENTER ACADEMIC PUBL JAPAN. 2-4-16 YAYOI, BUNKYO-KU, TOKYO, 113-0032, JAPAN. ISSN: 0301-4800. Pub. country: Japan. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Oral tolerance** is a potential strategy for preventing or minimizing aberrant immune responses. Although, **oral tolerance** has been extensively studied, to date the effects of dietary protein on the induction of **oral tolerance** are poorly understood. We have previously shown that restricted dietary protein induces **oral tolerance** to ovalbumin. This study was designed to investigate whether or not such tolerance occurs with beta-lactoglobulin (BLG) instead of ovalbumin (**OVA**) and if the tolerance resulting from this feeding regimen involves Th1-mediated immune response. Female BALB/c mice fed either 20% or 5% dietary protein were given 5 mg BLG or water orally for four consecutive days and then immunized intraperitoneally (ip) twice with BLG at 3-wk intervals. **Oral tolerance** induction was compared in BLG-fed and water-fed mice by measuring total IgE, BLG-specific antibodies, footpad reactions, splenocyte proliferation, and cytokine production. When mice were given BLG orally before ip immunization, the Th1-mediated immune responses (production of IL-2, IFN-gamma, and IgG2a) were significantly reduced, whereas the Th2-mediated immune responses (production of IL-4 and IgG1) were unchanged. The Th1-mediated immune responses were markedly down-regulated in mice fed 5% protein as compared to those in mice fed 20%, protein. Moreover, the production of total IgE, BLG-specific IgE, splenocyte proliferation, and footpad reactions were more reduced in mice fed 5% protein than those in mice fed 20%,, protein. The present study provides evidence that dietary protein plays an important role in the induction of **oral tolerance** against BLG as the result of, clear down-regulation of Th1 helper activity accompanied by a reduction in IgE.

L36 ANSWER 10 OF 42 MEDLINE on STN

2003333257. PubMed ID: 12864973. Neural correlates of IgE-mediated food **allergy**. Basso Alexandre Salgado; Pinto Frederico Azevedo Costa; Russo Momtchilo; Britto Luiz Roberto Giorgetti; de Sa-Rocha Luiz Carlos; Palermo Neto Joao. (Department of Pathology, School of Veterinary Medicine, University of Sao Paulo, Av. Prof. Dr. Orlando Marques de Paiva, 87, 05508-900, Sao Paulo, Brazil.. jpalermo@usp.br) . Journal of neuroimmunology, (2003 Jul) 140 (1-2) 69-77. Journal code: 8109498. ISSN: 0165-5728. Pub. country: Netherlands. Language: English.

AB Although many authors have considered the possibility of a direct interaction between food **allergy** and behavioral changes, the evidence supporting this hypothesis is elusive. Here, we show that after oral ovalbumin (**OVA**) challenge, allergic mice present higher levels of anxiety, increased Fos expression in emotionality-related brain areas, and aversion to **OVA**-containing solution. Moreover, treatment with anti-IgE antibody or induction of **oral tolerance** abrogate both food aversion and the expression of c-fos in the central nervous system (CNS). Our findings establish a direct relationship between brain function and food **allergy**, thus creating a solid ground for understanding the etiology of psychological disorders in allergic patients.

L36 ANSWER 11 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

2002:620054 Document No. 138:180376 Effects of the aqueous extract of Epimedii Herba on the induction of **oral tolerance** in mice. Kim, Joung-Hoon; Mun, Yeun-Ja; Im, Sook-Jung; Lee, Seung-Yon; Lee,

Sung-Won; Woo, Won-Hong (Department of Herbal Resources, Professional Graduate School of Oriental Medicine, Wonkwang University, Chunbuk, 570-749, S. Korea). Biological & Pharmaceutical Bulletin, 25(8), 1000-1005 (English) 2002. CODEN: BPBLEO. ISSN: 0918-6158. Publisher: Pharmaceutical Society of Japan.

AB We investigated the effects of the aqueous extract of Epimedii Herba (AEEH) on the induction of **oral tolerance**. **Oral tolerance** was induced in mice by giving an oral administration of 20 mg ovalbumin (**OVA**) 7 d before immunization with the antigen. AEEH at 40 mg/kg was given orally daily for 6 d from 24 h after the feeding of **OVA**. The results showed that oral administration of **OVA** greatly suppressed total serum and antigen-specific Ig levels, phagocytic activity and delayed-type hypersensitivity (DTH) reaction to the antigen. The suppression of these immune responses to **OVA** by the oral antigen was associated with a marked reduction of the production of interferon-γ (IFN-γ) and interleukin-4 (IL-4) from spleen cells. However, AEEH treatment significantly blocked the suppression of total serum and antigen-specific IgG2a antibodies, phagocytic activity and DTH response by the oral **OVA**. The suppression of IFN-γ production by the oral antigen was also greatly decreased by AEEH treatment. Therefore, AEEH appears to be effective in preventing the induction of **oral tolerance** to **OVA**.

L36 ANSWER 12 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2002:334029 The Genuine Article (R) Number: 541QB. Inhalation of a harmless antigen (ovalbumin) elicits immune activation but divergent immunoglobulin and cytokine activities in mice. Swirski F K; Gajewska B U; Alvarez D; Ritz S A; Cundall M J; Cates E C; Coyle A J; Gutierrez-Ramos J C; Inman M D; Jordana M; Stampfli M R (Reprint). McMaster Univ, Dept Pathol & Mol Med, Hlth Sci Ctr, Div Resp Dis, Room 4H21A, 1200 Main St W, Hamilton, ON L8N 3Z5, Canada (Reprint); McMaster Univ, Dept Pathol & Mol Med, Hlth Sci Ctr, Div Resp Dis, Hamilton, ON L8N 3Z5, Canada; McMaster Univ, Ctr Gene Therapeut, Hamilton, ON L8N 3Z5, Canada; Millennium Pharmceut, Cambridge, MA USA; McMaster Univ, Dept Med, Hamilton, ON L8N 3Z5, Canada. CLINICAL AND EXPERIMENTAL ALLERGY (MAR 2002) Vol. 32, No. 3, pp. 411-421. Publisher: BLACKWELL PUBLISHING LTD. P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND. ISSN: 0954-7894. Pub. country: Canada; USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background Exposure to aerosolized harmless antigen such as ovalbumin (**OVA**) has previously been shown to induce inhalation tolerance, a state characterized by inhibition of IgE synthesis and airway inflammation, upon secondary immunogenic antigen encounter. Immune events associated with this phenomenon are still poorly understood.

Objective The aim of this study was to investigate cellular and molecular mechanisms underlying this state of 'unresponsiveness'.

Methods; After initial repeated **OVA** exposure, mice were subjected to a protocol of antigen-induced airway inflammation, encompassing two intraperitoneal injections of **OVA** adsorbed to aluminium hydroxide followed by airway challenge. We assessed immune events in the draining lymph nodes after sensitization, and in the lungs after challenge.

Results In animals initially exposed to **OVA**, we observed, at the time of sensitization, considerable expansion of T cells, many of which expressed the activation markers CD69 and CD25, as well as increased numbers of antigen-presenting cells, particularly B cells. While these animals produced low levels of IgE, the observed elevated levels of IgG1 signified isotype switching. Splenocytes and lymph node cells from **OVA**-exposed mice produced low levels of IL-4, IL-5, IL-13 and IFN-gamma, indicating aborted effector function of both T helper (Th)2- and Th1-associated cytokines. Real time quantitative polymerase chain reaction (PCR) (TaqMan) analysis of costimulatory molecules in the lungs after in vivo challenge showed that B7.1, B7.2, CD28 and CTLA-4 mRNA

expression was low in animals initially exposed to **OVA**. Ultimately, these events were associated with abrogated airway inflammation and attenuated airway hyper-responsiveness. The decreased inflammation was antigen-specific and independent of IL-10 or IFN-gamma.

Conclusion Initial exposure to **OVA** establishes a programme that prevents the generation of intact, fully functional inflammatory responses upon secondary antigen encounter. The absence of inflammation, however, is not associated with categorical immune unresponsiveness.

L36 ANSWER 13 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

2002:520031 Document No. 137:272954 Suppression of IgE antibody response in mice by a polysaccharide, Az9, produced by Klebsiella oxytoca strain TNM3. Sugihara, Ryosuke; Matsumoto, Yuki; Ohmori, Hitoshi (Tayca Corporation, Osaka, 551-0022, Japan). Immunopharmacology and Immunotoxicology, 24(2), 245-254 (English) 2002. CODEN: IITOEF. ISSN: 0892-3973. Publisher: Marcel Dekker, Inc..

AB A soil bacterium, Klebsiella oxytoca TNM3, was found to produce a polysaccharide named AZ9 that shows suppressive effects on IgE antibody response in mice. When mice were administered with 50.apprx.100 mg/kg AZ9 s.c. for 4 consecutive days after immunization with trinitrophenyl (TNP)-keyhole limpet hemocyanin, anti-TNP IgE production was significantly suppressed, while the level of anti-TNP IgM was affected marginally. In AZ9-administered mice, IL-4 secretion from splenic cells was reduced to .apprx.30% of the untreated control. Thus, AZ9 suppression of IgE production may be due to attenuating effects on the Th2-type response. Although oral administration of AZ9 alone had no effects on IgE production, ovalbumin (**OVA**)-induced **oral tolerance** of anti-TNP IgE response to TNP-**OVA** was markedly augmented when a suboptimal dose of **OVA** was administered orally in combination with AZ9. Collectively, our data suggest that AZ9 has beneficial suppressive effects on IgE-dependent allergic responses.

L36 ANSWER 14 OF 42 MEDLINE on STN

2002283170. PubMed ID: 12026189. Low-protein diet induces **oral tolerance** to ovalbumin in mice. Satter Mohammed A; Sakai Kentaro; Ahmed Sherin; Yoshino Kenji; Yamamoto Shigeru; Shimizu Yuji; Ota Fusao. (Department of Food Microbiology, School of Nutrition, The University of Tokushima, Japan.) Journal of nutritional science and vitaminology, (2002 Feb) 48 (1) 51-8. Journal code: 0402640. ISSN: 0301-4800. Pub. country: Japan. Language: English.

AB The suitable development of **oral tolerance** against ingested dietary foods is of critical importance to escaping food **allergy**. Using mice as an animal model for **oral tolerance** against ovalbumin (**OVA**) as a dietary antigen, we investigated the effects of dietary protein on their immunological tolerance. Female BALB/c mice fed either a 20% or 5% protein diet were orally administered 5 mg of **OVA** for four consecutive days, then immunized intraperitoneally with 100 microg of **OVA**. The immunized group of mice were fed and treated in the same manner, except that they received orally distilled water for four consecutive days before receiving intraperitoneal immunization with the antigen. Immunization alone with **OVA** elevated the total IgE and induced the production of **OVA**-specific antibodies IgE, IgG, IgG1, and IgG2a in the sera of both the 20% and 5% protein diet groups. The oral administration of **OVA** to mice before intraperitoneal immunization significantly reduced the total IgE and **OVA**-specific antibodies in mice fed 5% protein diet, but it had hardly any effect on those in mice fed a 20% protein diet. When spleen cells from these groups of mice were cultured with **OVA** as a mitogen, they responded substantially to **OVA** in the immunized groups fed 20% and 5% protein diets and in the presensitized group fed 20% protein, but those from the presensitized group fed a 5% protein diet did not respond. Furthermore, when IL-4 was assayed in the spleen cell cultures of the 20% and 5% groups, mice in the

presensitized group fed a 5% protein diet produced a significantly less amount of IL-4 than those fed a 20% protein diet. Moreover, irrelevant to the protein amount in the diet, the production of IFN-gamma from spleen cell cultures dramatically decreased in the group without presensitization and profoundly increased in the presensitized group of mice fed a 5% protein diet. These findings suggest that a low-protein diet leads to an induction of **oral tolerance** against dietary antigens; this appears to involve a clear down-regulation of Th2 cytokine, IL-4.

L36 ANSWER 15 OF 42 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2001361383 EMBASE Activation of CD25(+)CD4(+) regulatory T cells by oral antigen administration. Zhang X.; Izikson L.; Liu L.; Weiner H.L.. Dr. H.L. Weiner, Center for Neurologic Diseases, Harvard Medical School, Brigham and Women's Hospital, 77 Avenue Louis Pasteur, Boston, MA 02115, United States. hweiner@rics.bwh.harvard.edu. Journal of Immunology 167/8 (4245-4253) 15 Oct 2001.
Refs: 41.
ISSN: 0022-1767. CODEN: JOIMA3. Pub. Country: United States. Language: English. Summary Language: English.

AB CD25(+)CD4(+) T cells are naturally occurring regulatory T cells that are anergic and have suppressive properties. Although they can be isolated from the spleens of normal mice, there are limited studies on how they can be activated or expanded in vivo. We found that oral administration of **OVA** to **OVA** TCR transgenic mice resulted in a modification of the ratio of CD25(+)CD4(+) to CD25(-)CD4(+) cells with an increase of CD25(+)CD4(+) T cells accompanied by a decrease of CD25(-)CD4(+) T cells. The relative increase in CD25(+)CD4(+) T cells persisted for as long as 4 wk post feeding. We also found that CTLA-4 was dominantly expressed in CD25(+)CD4(+) T cells and there was an increase in the percentage of CD25(+)CD4(+) T cells expressing CTLA-4 in **OVA** -fed mice. In contrast to CD25(-)CD4(+) cells, CD25(+)CD4(+) cells from fed mice proliferated only minimally to **OVA** or anti-CD3 and secreted IL-10 and elevated levels of TGF-β(1) following anti-CD3 stimulation. CD25(+)CD4(+) cells from fed mice suppressed the proliferation of CD25(-)CD4(+) T cells in vitro more potently than CD25(+)CD4(+) T cells isolated from unfed mice, and this suppression was partially reversible by IL-10 soluble receptor or TGF-β soluble receptor and high concentration of anti-CTLA-4. With anti-CD3 stimulation, CD25(+)CD4(+) cells from unfed mice secreted IFN-??, whereas CD25(+)CD4(+) cells from fed mice did not. Adoptive transfer of CD25(+)CD4(+) T cells from fed mice suppressed in vivo delayed-type hypersensitivity responses in BALB/c mice. These results demonstrate an Ag-specific in vivo method to activate CD25(+)CD4(+) regulatory T cells and suggest that they may be involved in **oral tolerance**.

L36 ANSWER 16 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

2001:222641 Document No. 134:365684 Peyer's patches are required for **oral tolerance** to proteins. Fujihashi, Kohtaro; Dohi, Taeko; Rennert, Paul D.; Yamamoto, Masafumi; Koga, Toshiya; Kiyono, Hiroshi; McGhee, Jerry R. (Department of Oral Biology and The Immunobiology Vaccine Center, Birmingham Medical Center, University of Alabama, Birmingham, AL, 35294-2170, USA). Proceedings of the National Academy of Sciences of the United States of America, 98(6), 3310-3315 (English) 2001. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.

AB To clarify the role of Peyer's patches in **oral tolerance** induction, BALB/c mice were treated in utero with lymphotoxin β-receptor Ig fusion protein to generate mice lacking Peyer's patches. When these Peyer's patch-null mice were fed 25 mg of ovalbumin (**OVA**) before systemic immunization, **OVA**-specific IgG Ab responses in serum and spleen were seen, in marked contrast to low responses in **OVA**-fed normal mice. Further, high

T-cell-proliferative- and delayed-type hypersensitivity responses were seen in Peyer's patch-null mice given oral **OVA** before systemic challenge. Higher levels of CD4+ T-cell-derived IFN-γ, IL-4, IL-5, and IL-10 syntheses were noted in Peyer's patch-null mice fed **OVA**, whereas **OVA**-fed normal mice had suppressed cytokine levels. In contrast, oral administration of trinitrobenzene sulfonic acid (TNBS) to Peyer's patch-null mice resulted in reduced TNBS-specific serum Abs and splenic B cell antitrinitrophenyl Ab-forming cell responses after skin painting with picryl chloride. Further, when delayed-type hypersensitivity and splenic T cell proliferative responses were examined, Peyer's patch-null mice fed TNBS were unresponsive to hapten. Peyer's patch-null mice fed trinitrophenyl-**OVA** failed to induce systemic unresponsiveness to hapten or protein. These findings show that organized Peyer's patches are required for **oral tolerance** to proteins, whereas haptens elicit systemic unresponsiveness via the intestinal epithelial cell barrier.

L36 ANSWER 17 OF 42 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2001085833 EMBASE Development of the susceptibility to **oral tolerance** induction in infant mice administered a herbal drug, Hochu-ekki-to (Bu-Zhong-Yi-Qi-Tang). Kaneko M.; Kawakita T.; Yamaoka Y.; Nomoto K.. T. Kawakita, Kampo (Traditional Japan. Medicine), Healthcare Research Laboratories, Kanebo Co. Ltd., 1-5-90 Tomobuchi-cho, Miyakojima-ku, Osaka 534-0016, Japan. International Immunopharmacology 1/2 (219-227) 2001.
Refs: 32.
ISSN: 1567-5769. CODEN: IINMBA.
Publisher Ident.: S 1567-5769(00)00022-9. Pub. Country: Netherlands.
Language: English. Summary Language: English.

AB The susceptibility to **oral tolerance** in post-neonatal infant mice and the effect of a herbal drug, Hochu-ekki-to (HOT), on the susceptibility were investigated. To induce **oral tolerance** induction, infant and adult mice at 4 and 8 weeks of age, respectively, were orally administered a single high dose of **OVA** before an intraperitoneal immunization with **OVA** adsorbed on aluminum hydroxide. HOT (1000 mg/kg) was administered orally for 7 days before the induction. HOT significantly decreased the serum levels of **OVA**-specific IgE and IgG1 and the antigen-specific proliferation of spleen cells in infant mice, both of which were greatly enhanced compared to in adult mice. HOT increased the number of both CD4(+) T cells and antigen-presenting cells expressing MHC class II as well as costimulatory molecules (CD40, CD80 and/or CD86) in the Peyer's patch (PP) of infant mice, which had fewer cells than adult mice. In the PP, moreover, HOT augmented the IL-12p40 mRNA expression and spontaneous or CD40-stimulated IL-12 production, and increased the number of CD4(+) cells expressing CD40 ligand, which is up regulated by IL-12. These results suggest that HOT increases the number and improves the function of PP cells that are fully susceptible to the induction of **oral tolerance**. .COPYRGT. 2001 Elsevier Science B.V.

L36 ANSWER 18 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

2001:755905 Document No. 136:324699 Effect of low protein diet on oral tolerization. Sakai, Kentaro; Satter, Mohammed A.; Ota, Fusao; Yamamoto, Shigeru (Department of Nutrition, School of Medicine, university of Tokushima, Tokushima, 770-8503, Japan). Hissu Aminosan Kenkyu, 161, 88-92 (Japanese) 2001. CODEN: HAMKE3. ISSN: 0387-4141. Publisher: Hissu Aminosan Kenkyu Iinkai.

AB In order to study the effect of low protein diet on oral tolerization in relation to food **allergy**, mice were fed with a diet containing 20 or 5 % proteins for 6 wk and orally administered ovalbumin (**OVA**, 10 mg/mL) for 4 days with/without of following immunization by **OVA**, and serum Igs (IgE, IgG, IgG1, and IgG2a), splenocyte proliferation, and

IL-4 production from splenocytes in the mice were analyzed. The results suggested increased **oral tolerance** by low-protein diet.

L36 ANSWER 19 OF 42 MEDLINE on STN

2000385105. PubMed ID: 10848926. Prolonged oral treatment with low doses of allergen conjugated to cholera toxin B subunit suppresses immunoglobulin E antibody responses in sensitized mice. Rask C; Holmgren J; Fredriksson M; Lindblad M; Nordstrom I; Sun J B; Czerkinsky C. (Department of Medical Microbiology and Immunology, Goteborg University, Goteborg, Sweden.) Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology, (2000 Jul) 30 (7) 1024-32. Journal code: 8906443. ISSN: 0954-7894. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: **Oral tolerance** is a long recognized method for inducing systemic immunological tolerance. However, large doses of antigen and frequent administrations are often required. By linking the antigen to the nontoxic mucosa-binding B subunit of cholera toxin (CTB), the required amount can be dramatically reduced. We have previously shown that mucosal administration of small amounts of antigens coupled to CTB can suppress peripheral Th1 cell-reactivity and associated inflammatory immunopathology in both naive and systemically-immunized animals. Induction of **oral tolerance** by repeated feeding of relatively small doses of antigen has, in some cases been shown to involve the generation of regulatory Th2-like CD4+ T cells, and hence could promote rather than suppress type I immunoglobulin (Ig) E-mediated allergic responses. OBJECTIVES: We examined whether oral prophylactic or therapeutic administration of a model allergen coupled to CTB would modulate allergen-specific IgE responses in high IgE responder Balb/c mice. METHODS: Ovalbumin (**OVA**) was used as a model allergen. Mice were treated perorally with free or CTB-coupled **OVA** before or after systemic priming with alum-adsorbed **OVA**. Allergen-specific IgE levels in serum were measured with the passive cutaneous anaphylaxis test at various time-points. RESULTS: Oral administration of a single low dose of CTB-linked **OVA**, prior to systemic sensitization and challenge with **OVA**, suppressed allergen-specific serum IgE antibody responses. Treatment with comparable doses of free **OVA** was much less effective. Most importantly, oral treatment with CTB-**OVA** conjugate could also suppress an already initiated IgE antibody response, but to achieve such a 'therapeutic effect', administration of multiple low doses of conjugate over a long time was required. Oral treatment with CTB-**OVA** conjugate could also effectively suppress antigen-specific Th1-mediated delayed-type hypersensitivity. Thus treatment with a CTB-conjugated model allergen can affect a broad range of T-cell-driven immune responses, even in antigen-experienced animals. CONCLUSION: These results may impact on the development of therapeutic vaccines against type I **allergies**.

L36 ANSWER 20 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2000:321370 The Genuine Article (R) Number: 306PB. Serum IgE response to orally ingested antigen: A novel IgE response model with allergen-specific T-cell receptor transgenic mice. Shida K (Reprint); Hachimura S; Ametani A; Ishimori M; Ling M; Hashiguchi M; Ueda Y; Sato T; Kumagai Y; Takamizawa K; Habu S; Kaminogawa S. YAKULT CENT INST MICROBIOL RES, 1796 YAHO, KUNITACHI, TOKYO 1868650, JAPAN (Reprint); UNIV TOKYO, DEPT APPL BIOL CHEM, TOKYO, JAPAN; TOKAI UNIV, SCH MED, DEPT IMMUNOL, ISEHARA, KANAGAWA 25911, JAPAN; RES DEV CORP JAPAN, PRECURSORY RES EMBRYON SCI & TECHNOL, YOKOHAMA, KANAGAWA, JAPAN. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (APR 2000) Vol. 105, No. 4, pp. 788-795. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: JAPAN. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: The mechanism by which orally ingested allergens elicit an IgE response remains unclear because there are few animal models available for investigation of this response.

Objective: We tried to develop a murine model suitable for investigation of the IgE response to orally ingested allergens, which would allow us to identify T cells that could promote IgE production.

Methods: Ovalbumin (**OVA**)-specific T-cell receptor transgenic mice were fed a diet containing **OVA**, and both the serum antibody response and cytokine production by splenocytes were examined.

Results: Oral administration of **OVA** to transgenic mice Led to an increase in the levels of both antigen-specific IgE and total IgE in the sera. Subsequent intravenous challenge of **OVA**-fed transgenic mice with **OVA** resulted in anaphylactic shock. Analysis of cytokine production by splenocytes revealed that high IL-4-producing T cells appeared in the spleen 1 week after the start of feeding the **OVA** diet. T cells from these mice were found to promote IgE secretion by BALB/c B cells in vitro. This helper activity and the levels of IL-4 secretion were diminished after long-term feeding. These findings suggest the possibility that the orally ingested antigen elicited a response by a subpopulation of T cells that produce high levels of T-H2-type cytokines and that promote IgE secretion, and these same T cells were tolerized by the orally ingested antigen.

Conclusion: This experimental model with transgenic mice may be a useful tool for further studies of the cellular and molecular mechanisms of the T-cell and IgE responses to orally ingested antigens.

L36 ANSWER 21 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:622438 The Genuine Article (R) Number: 343NH. Mechanisms preventing allergen-induced airways hyperreactivity: Role of tolerance and immune deviation. Tsitoura D C; Blumenthal R L; Berry G; DeKruyff R H; Umetsu D T (Reprint). STANFORD UNIV, MED CTR, DEPT PEDIAT, DIV CLIN IMMUNOL & ALLERGY, RM G309, STANFORD, CA 94305 (Reprint); STANFORD UNIV, MED CTR, DEPT PEDIAT, DIV CLIN IMMUNOL & ALLERGY, STANFORD, CA 94305; STANFORD UNIV, DIV IMMUNOL & TRANSPLANTAT BIOL, STANFORD, CA 94305; STANFORD UNIV, DEPT PATHOL, STANFORD, CA 94305. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (AUG 2000) Vol. 106, No. 2, pp. 239-246. Publisher: MOSBY, INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Aeroallergens continuously enter the respiratory tract of atopic individuals and provoke the development of asthma characterized by airway hyperreactivity; (AHR) and inflammation, By contrast, nonatopic individuals are exposed to the same aeroallergens, but airway inflammation does not develop, However, the mechanisms that prevent allergen-induced respiratory diseases in nonatopic subjects are poorly characterized.

Objective: In this study we compared the role of allergen-specific T-cell tolerance and immune deviation in conferring protection against the development of allergen-induced AHR,

Methods: We exposed mice to intranasal ovalbumin (**OVA**) to induce T-cell tolerance and examined its effects on the subsequent development of AHR and inflammation.

Results: We demonstrated that exposure of mice to intranasal **OVA** resulted in peripheral CD4(+) T-cell unresponsiveness that very efficiently prevented not only the development of AHR but also greatly inhibited airway inflammation and **OVA**-specific IgE production. The induction of peripheral T-cell tolerance and protection against AHR were not dependent on the presence of IFN-gamma or IL-4, The development of AHR was also prevented by an **OVA**-specific T(H)1-biased immune response induced by inhalation of **OVA** in the presence of IL-12, However, the **OVA**-specific T(H)1 response was associated with a significant degree of pulmonary inflammation.

Conclusion: These results indicate that both allergen-specific T-cell tolerance and T(H)1-biased immune deviation prevent the development of

AHR, but T(H)1 responses are associated with significantly greater inflammation in the lung than is associated with T-cell unresponsiveness. Therefore CD4(+) T-cell unresponsiveness critically regulates immune responses to aeroallergens and protects against the development of allergic disease and asthma.

L36 ANSWER 22 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:221190 The Genuine Article (R) Number: 293KD. Suppression of specific IgE antibody responses by liposome-conjugated ovalbumin in mice sensitized with ovalbumin via the respiratory tract. Yoshikawa T; Uchida T; Naito S; Horino A; Taneichi M; Kato H; Komuro K; Nakano Y; Mori M; Nishinohara S; Chiba J; Kurata T; Tamura S (Reprint). NATL INST INFECT DIS, DEPT PATHOL, SHINJUKU KU, TOYAMA 1-23-1, TOKYO 1628640, JAPAN (Reprint); NATL INST INFECT DIS, DEPT PATHOL, SHINJUKU KU, TOKYO 1628640, JAPAN; NATL INST INFECT DIS, DEPT SAFETY RES BIOL, SHINJUKU KU, TOKYO 1628640, JAPAN; NOF CORP, TSUKUBA RES LAB, CHIBA, JAPAN; SCI UNIV TOKYO, IMMUNOL LAB, CHIBA, JAPAN. INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY (FEB 2000) Vol. 121, No. 2, pp. 108-115. Publisher: KARGER. ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND. ISSN: 1018-2438. Pub. country: JAPAN. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Background: Previously we have shown that intranasal administration of ovalbumin (**OVA**) together with cholera toxin (CT) abrogates nasal tolerance to **OVA**, resulting in the induction of specific IgE antibody (Ab) responses, and that intraperitoneal injection of **OVA** coupled with liposomes (**OVA**-liposomes) induces a selective suppression of IgE Ab responses to **OVA**. Whether **OVA** -liposomes suppress anti-**OVA** IgE Ab responses in mice sensitized with CT-combined **OVA** via the respiratory tract remains to be clarified. Methods: In some experiments, mice were given **OVA**, liposomes or **OVA**-liposomes with or without CT intranasally three times, at 2-week intervals (weeks 0, 2 and 4). In other experiments, mice were given **OVA**-liposomes intranasally 2 days before or 1 and 3 weeks after CT-combined **OVA** (week 0), which was administered intranasally three times, at 2-week intervals (weeks 0, 2 and 4). Two weeks after the third administration of CT-combined **OVA** (week 0), nasal wash and serum IgA, IgG and IgE Ab responses were assayed. Results: Pretreatment: with **OVA**-liposomes suppressed IgE Ab responses to CT-combined **OVA**, with a significantly high production of: both nasal IgA and serum IgG Absolute Moreover, treatment with **OVA**-liposomes 1 and 3 weeks after CT-combined **OVA** administration also suppressed IgE Ab responses. The suppression of anti-**OVA** IgE Ab production by **OVA**-liposomes was accompanied by a simultaneous enhancement of specific IgA and IgG (IgG1, and especially IgG2a) Ab production. Conclusions: Postimmunization treatment with **OVA**-liposomes, as well as preimmunization treatment, suppressed specific IgE Ab responses in mice sensitized intranasally with CT-combined **OVA**. Allergens conjugated to liposomes may be appropriate for preventing the development of **allergies** to inhaled or dietary antigens in humans. Copyright (C) 2000 S. Karger AG, Basel.

L36 ANSWER 23 OF 42 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
1999049760 EMBASE Immunoglobulin E suppression and cytokine modulation in mice orally tolerized to β-lactoglobulin. Pecquet S.; Pfeifer A.; Gauldie S.; Fritsche R.. Dr. S. Pecquet, Food Immunology, Nestle Research Centre, BP44, CH 1000 Lausanne 26, Switzerland. Immunology 96/2 (278-285) 1999.
Refs: 32.
ISSN: 0019-2805. CODEN: IMMUAM. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB This study was designed to confirm the tolerogenic properties of β-

lactoglobulin in a mouse model and to assess specific **oral tolerance** induction in humoral and cellular compartments. BALB/c mice were fed β- lactoglobulin (BLG) or whey proteins at different ages and subsequently intraperitoneally challenged 5 days later with both BLG and a non-specific antigen, ovalbumin (**OVA**). Three weeks later, **oral tolerance** induction was analysed in CMP-fed, versus saline-fed mice, by measuring specific seric and intestinal antibody responses, delayed-type hypersensitivity (DTH), specific splenocyte proliferation, and cytokine secretion patterns. Three-week-old mice fed high doses of either whey proteins or BLG (respectively 3 mg/g or 5 mg/g of body weight) were found to achieve oral tolerization. At humoral and mucosal levels, anti-BLG immunoglobulin E (IgE) were suppressed in these groups when compared with saline fed mice. With respect to cellular responses, systemic DTH and lymphocyte proliferation to BLG were also inhibited in CMP-fed mice. Weaning time was determined to be the best period for **oral tolerance** induction. Kinetic analyses showed however, that a minimum of 2 weeks was required for **oral tolerance** detection. Finally, cytokine profiles indicated a reciprocal decrease of interleukin-2 (IL-2) and interferon-γ (IFN-γ) versus an increase of IL-10 and transforming growth factor-β (TGF-β) secretions in tolerized mice. Taken together, these results clearly showed that oral administration of high doses of cows' milk proteins can induce significant hyposensitization in mice, in a specific inhibition of T helper 1 (Th1) lymphocytes with the participation of suppressor cytokines.

L36 ANSWER 24 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:653370 The Genuine Article (R) Number: 227JF. Transforming growth factor-beta secreted from CD4(+) T cells ameliorates antigen-induced eosinophilic inflammation - A novel high-dose tolerance in the trachea. Haneda K; Sano K; Tamura G; Shirota H; Ohkawara Y; Sato T; Habu S; Shirato K (Reprint). TOHOKU UNIV, SCH MED, DEPT INTERNAL MED 1, AOBA KU, SENDAI, MIYAGI 98077, JAPAN (Reprint); TOHOKU UNIV, SCH MED, DEPT INTERNAL MED 1, AOBA KU, SENDAI, MIYAGI 98077, JAPAN; TOKAI UNIV, SCH MED, DEPT IMMUNOL, ISEHARA, KANAGAWA 25911, JAPAN. AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY (AUG 1999) Vol. 21, No. 2, pp. 268-274. Publisher: AMER LUNG ASSOC. 1740 BROADWAY, NEW YORK, NY 10019. ISSN: 1044-1549. Pub. country: JAPAN. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The induction of peripheral tolerance is one of the feasible approaches for the control of autoimmunities and **allergies**. Tolerance induction in the intestine has been studied extensively and therapeutic applications to autoimmunities are in progress, whereas tolerance in the respiratory tract is poorly investigated. We examined the immunoregulatory mechanisms for evading exaggerated inflammatory responses in the murine airway mucosa. Administration of an optimal dose of ovalbumin (**OVA**) to the trachea elicited eosinophilic inflammation in the trachea of **OVA**/aluminum hydroxide-sensitized BALB/c mice, whereas higher doses were unable to do so. This failure paralleled the downregulation of interleukin-4 production by mediastinal lymph node (LN)T cells. This high-dose tolerance was attributable to the mechanisms of antigen (Ag)-specific suppression, because the adoptive transfer of CD4(+) LN T cells from the **OVA**-tolerant mice inhibited the **OVA**-specific, but not irrelevant Ag KLH-specific, eosinophilic responses. The inhibitory effects were neutralized by the intratracheal administration of anti-transforming growth factor (TGF)-beta, but not that of anti-interferon (IFN)-gamma, monoclonal antibodies, indicating that the high-dose tolerance was mediated by secreted TGF-beta, but not by the dominance of transferred T helper (Th)1 cells over Th2 cells. The pivotal role of TGF-beta was reinforced by the finding that the LN cells from the **OVA**-tolerant mice produced TGF-beta in response to the in vitro Ag stimulation. These results demonstrate a novel regulatory mechanism in the airway: that TGF-beta secreted by T cells plays an important role in the

downmodulation of the immune responses to high doses of Ag which might otherwise induce deleterious inflammation in the airway mucosal tissues.

L36 ANSWER 25 OF 42 MEDLINE on STN
1999344622. PubMed ID: 10416133. **Oral tolerance** by a high dose **OVA** in BALB/c mice is more pronounced and persistent in Th2-mediated immune responses than in Th1 responses. Kang B; Kim K M; Kang C Y. (Laboratory of Immunology, College of Pharmacy, Seoul National University, Korea.) Immunobiology, (1999 Jun) 200 (2) 264-76. Journal code: 8002742. ISSN: 0171-2985. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Oral administration of antigen induces an antigen-specific immunologic tolerance and many studies are being carried out to apply this phenomenon to the treatment of autoimmune diseases. In this study, we investigated long-term Th1 and Th2 tolerance in mice given a high dose of orally administered Ovalbumin (**OVA**). Feeding **OVA** to BALB/c mice suppressed **OVA**-specific IgG response and the degree of inhibition was dose-dependent in the range of 2.5-250 mg. Moreover, the state of tolerance established by prior feeding of high dose of **OVA** was present after 26 weeks. Interestingly, even though both Th subsets were tolerized significantly for a short period, the tolerizing effect was more pronounced and persistent in Th2-mediated immune responses. Thus we speculate that oral administration of a single high dose of **OVA** induces Th1- and Th2-tolerance by different mechanisms. Our findings could be important in the development of therapeutics for the treatment of autoimmune disease and **allergy** .

L36 ANSWER 26 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:865510 The Genuine Article (R) Number: 252UJ. Development of immunoglobulin G and immunoglobulin E antibodies to cow's milk proteins and ovalbumin after a temporary neonatal exposure to hydrolyzed and whole cow's milk proteins. Juvonen P (Reprint); Mansson M; Kjellman N I M; Bjorksten B; Jakobsson I. ODENSE UNIV HOSP, DEPT PAEDIAT, DK-5000 ODENSE, DENMARK (Reprint); UNIV LUND HOSP, DEPT EXPT RES, MALMO, SWEDEN; LINKOPING UNIV HOSP, DEPT PAEDIAT, S-58185 LINKOPING, SWEDEN; UNIV LUND HOSP, DEPT PAEDIAT, S-22185 LUND, SWEDEN. PEDIATRIC ALLERGY AND IMMUNOLOGY (AUG 1999) Vol. 10, No. 3, pp. 191-198. Publisher: MUNKSGAARD INT PUBL LTD. 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK. ISSN: 0905-6157. Pub. country: DENMARK; SWEDEN. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The ingestion of food antigens usually results in the induction of **oral tolerance**, but the clinical and immunologic consequences of brief exposure to cow's milk proteins during the neonatal period are not well-documented. The aim of this work was to study immunoglobulin (Ig)E and IgG responses to cow's milk proteins and ovalbumin after exposure during the first three days of life in infants who were otherwise exclusively breast-fed. A group of 129 infants was randomly assigned at birth to one of three feeding regimens: human milk (HM), cow's milk formula (CMF), or a casein hydrolysate formula (CHF), during the first three days of life. They were then all exclusively breast-fed for a varying period of time and followed for two years. Serum IgG and IgE antibodies to cow's milk proteins and ovalbumin (**OVA**) were analyzed in blood samples obtained at birth, at 4 days and at 2, 4, 8, 12 and 24 months of age. The levels of IgG antibodies to beta-lactoglobulin (IgG-BLG) and bovine serum albumin (IgG-BSA) were higher in the CMF and the HM groups than in the CHF group for up to two years. This was particularly obvious for IgG-BLG in infants who started weaning before two months, The levels of IgG antibodies to casein (IgG-CAS) were higher in the CMF goup, as compared with the CHF group at 8 and 12 months. The levels of IgG antibodies to **OVA** were similar in all three feeding groups. The levels of IgE antibodies to CAS or **OVA** were similar in the three feeding groups. Exposure to cow's

milk during the first three days of life stimulated IgG antibody production to cow's milk proteins and this was still obvious at 2 years of age, while feeding with a casein hydrolysate during the first three days of life was associated with low levels of IgG antibodies to cow's milk proteins.

L36 ANSWER 27 OF 42 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

1998373713 EMBASE Heat denaturation of egg-white proteins abrogates the induction of **oral tolerance** of specific TH2 immune responses in mice. Peng H.-J.; Chang Z.-N.; Tsai L.-C.; Su S.-N.; Shen H.-D.; Chang C.-H.. H.-J. Peng, Department of Medical Research, Veterans General Hospital, 201 Shih-Pai Road, Taipei 11217, Taiwan,Province of China. Scandinavian Journal of Immunology 48/5 (491-496) 1998.
Refs: 33.
ISSN: 0300-9475. CODEN: SJIMAX. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Human foods are usually prepared by cooking. Boiling of chicken egg- white (EW) led to decreased allergenicity, and abrogated intestinal uptake of immunoreactive ovalbumin (**OVA**) when fed to mice. Therefore, the effects of oral administration of boiled EW were examined further in BALB/c mice. Specific IgE, IgG(I) and IgG antibody responses were suppressed by raw EW, but not by EW boiled for 5 or 60 min, fed prior to sensitization with 10 μg **OVA** or 1 μg DNP- **OVA** in alum. Similar results were obtained when mice were sensitized with 10 μg conalbumin, ovomucoid or lysozyme in alum, BALB/c spleen cell proliferation and secretion of Th2 cytokines IL-4 and IL-5 during in vitro stimulation with **OVA** were also suppressed by feeding raw EW, but not by boiled EW. Although heat denaturation of proteins can minimize allergenicity, the present results suggest that over, cooking of proteins may affect their intestinal antigen processing and thus prevent the induction of **oral tolerance**.

L36 ANSWER 28 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

1998:362680 Document No. 129:148216 Chemical denaturation of ovalbumin abrogates the induction of **oral tolerance** of mouse reaginic antibody responses. Peng, H. -J.; Chang, Z. -N.; Lin, S. -Y.; Han, S. -H.; Chang, C. -H. (Department of Medical Research, Veterans General Hospital-Taipei, Taipei, 11217, Taiwan). Scandinavian Journal of Immunology, 47(5), 475-480 (English) 1998. CODEN: SJIMAX. ISSN: 0300-9475. Publisher: Blackwell Science Ltd..

AB The effect of chemical denaturation of ovalbumin (**OVA**) on the induction of **oral tolerance** of reaginic antibody responses was studied. Both urea-denatured **OVA** (UD-**OVA**) and carboxymethylated UD-**OVA** (CM-**OVA**) were purified by centrifugation. When compared with **OVA** and UD-**OVA**, CM-**OVA** had the least sensitizing capacity and allergenicity in IgE responses to **OVA**. BALB/c IgE, IgG1 and IgG antibody responses were suppressed by **OVA**, but not by UD-**OVA** or CM-**OVA**, fed prior to sensitization with **OVA**, UD-**OVA**, or CM-**OVA** in alum, resp. The priming effect of specific IgG and IgG1 antibody responses was induced by CM-**OVA** fed prior to sensitization with **OVA** or CM-**OVA**. The proliferation of BALB/c spleen cells and their secretion of T helper type 2 (Th2) cytokines interleukin-4 (IL-4) and IL-5 were also orally tolerized by **OVA**, but not by denatured **OVA**. Although denatured **OVA** is hypoallergenic, the present result indicates that denaturation of a soluble protein prevents the induction of **oral tolerance** of Th2 responses.

L36 ANSWER 29 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

1998:326961 Document No. 129:94174 Immunological consequences of intervention in established immune responses by feeding protein antigens.

Leishman, Andrew J.; Garside, Paul; Mowat, Allan McI. (Department of Immunology, Western Infirmary, University of Glasgow, Glasgow, GLL 6NT, UK). Cellular Immunology, 183(2), 137-148 (English) 1998. CODEN: CLIMB8. ISSN: 0008-8749. Publisher: Academic Press.

AB The usual result of feeding protein antigens to naive animals is the induction of profound immunol. unresponsiveness and this is currently being exploited to treat inflammatory disease. Because the most useful therapeutic application of feeding antigen would be to suppress established disease, the aim of this study was to compare the immunol. basis of **oral tolerance** induced by feeding a model antigen to naive and primed animals. The authors show that feeding 2-200 mg ovalbumin (**OVA**) to mice 7 days after immunization with **OVA** in adjuvant produces dose-dependent suppression of delayed-type hypersensitivity (DTH), T cell proliferation, and both TH1 and TH2 cytokines, although serum IgG levels were unaffected. Feeding **OVA** before immunization suppressed all these responses. Although feeding up to 8 days after immunization could suppress some subsequent responses, tolerance was induced much more effectively when antigen was fed in the first 4 days after immunization. Tolerance in primed mice was intact in IL-4-/- mice, indicating that it was not caused by selective upregulation of TH2 cells in vivo. The authors conclude that oral administration of protein antigen can inhibit ongoing responses by all effector T cell subsets, but the exact consequences, and therefore possibly the mechanisms, are different from those induced by tolerizing naive mice. These findings may have important implications for designing therapeutic regimes exploiting **oral tolerance**.

L36 ANSWER 30 OF 42 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

1998:212454 Document No.: PREV199800212454. Prevention of lung eosinophilic inflammation by **oral tolerance**. Russo, Momtchilo [Reprint author]; Jancar, Sonia; Siqueira, Ana Lucia Pereira De; Mengel, Jose; Gomes, Eliane; Ficker, Sabine Madsen; Faria, Ana Maria Caetano De. Dep. Imunol., Inst. Cienc. Biomedicas, ICB-III, Univ. de Sao Paulo, Av. Professor Lineu Prestes 2415, 05508-900 Sao Paulo, SP, Brazil. Immunology Letters, (March, 1998) Vol. 61, No. 1, pp. 15-23. print. CODEN: IMLED6. ISSN: 0165-2478. Language: English.

AB Airway inflammation plays a major role in human asthma. Increasing evidence points to a close correlation between eosinophil infiltration and allergic lung disease. A new murine model of eosinophilic lung inflammation has recently been developed; it consists of immunizing mice with small fragments of solidified hen egg white implanted (EWI) into the subcutaneous tissue. In this model, which is further characterized here, mice challenged with ovalbumin (**OVA**) present an intense and persistent lung eosinophilia, as well as histopathological findings that resemble human asthma. In the present work, the effect of **oral tolerance** on the development of allergic lung inflammation in B6 mice immunized with antigen plus adjuvant or with EWI is investigated. It was found that in mice rendered orally tolerant by previous exposure to antigen in the drinking water, the T-helper type 2 cell (Th2)-associated allergic responses in both protocols of immunization were almost completely abolished. The allergic responses were assessed by pulmonary and bone marrow eosinophilia, lung histopathology and antigen-specific IgE and IgG1 production. These findings provide the first indication that Th2-associated lung pathology can be prevented by **oral tolerance**.

L36 ANSWER 31 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

1998:789663 Document No. 130:152500 Priming or tolerance of the B- and Th2-dependent immune response by the oral administration of **OVA** -DNP is determined by the antigen dosage. Franco, Liliana; Benedetti, Ruben; Ferek, Guillermo Assad; Massouh, Ernesto; Flo, Juan (Laboratory Immunochemistry, Faculty Exact & Natural Sciences, University Buenos Aires, Buenos Aires, Argent.). Cellular Immunology, 190(1), 1-11

(English) 1998. CODEN: CLIMB8. ISSN: 0008-8749. Publisher: Academic Press.

AB In the present report we established antigen dosages that induce **oral tolerance** of Th1 and Th2 lymphocytes or instead prime B- and Th2-dependent immune response and induce the tolerance of Th1 lymphocytes. Using different hapten-carrier systems, we found that low doses of **OVA**-DNP administered orally primed B and Th2 cells. On the other hand, no priming of B or Th2 cells was found in high-dose-**OVA**-DNP-fed rats. Low-dose-**OVA**-DNP-fed rats showed a strong mucosal immune response, with a high number of IgA anti-DNP antibody-forming cells in the lamina propria, while no mucosal immune response was observed in high-dose-**OVA**-DNP-fed rats. Thirty days after the immunization, tolerance of Th1 lymphocytes was confirmed in low- and high-dose-**OVA**-DNP-fed rats by diminished antigen-specific proliferation in vitro, reduced titers of anti-DNP IgG2a in serum, reduced expression of CD25 and CD134 mols. in cultured cells exposed to the antigen, reduced DTH reaction, and reduced IL-2 synthesis in culture. On the other hand, a high dose of **OVA**-DNP led to Th1 and Th2 tolerance, with an inhibition of specific IgG1 and IgG2a anti-DNP antibodies in serum after a parenteral challenge with **OVA** in CFA. This functional evidence was supported by the direct examination of IL-2 and IL-4 production Furthermore, whereas in vitro assays seem to indicate that active suppression could be the responsible for Th1 tolerance in low-dose-**OVA**-DNP-fed rats, the results obtained after the transfer of spleen or MLN cells to naive recipients support the idea that a subtractive mechanism is behind the tolerance of Th1 lymphocytes. (c) 1998 Academic Press.

L36 ANSWER 32 OF 42 MEDLINE on STN

1998026170. PubMed ID: 9379048. TGF-beta induced by **oral tolerance** ameliorates experimental tracheal eosinophilia. Haneda K; Sano K; Tamura G; Sato T; Habu S; Shirato K. (First Department of Internal Medicine, Tohoku University School of Medicine, Sendai, Japan.) Journal of immunology (Baltimore, Md. : 1950), (1997 Nov 1) 159 (9) 4484-90. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Induction of peripheral tolerance is one of the feasible approaches for the control of autoimmunities and **allergies**. Therapeutic applications of **oral tolerance** to autoimmunities are in progress both experimentally and clinically, while those to **allergies** have been poorly investigated. We examined the induction of CD4+ T cells with suppressive properties by **oral tolerance** and the mechanism by which these cells down-regulated Ag-induced eosinophilia in the trachea. Feeding of mice transgenic for anti-**OVA** TCR with high doses of **OVA** inhibited the airway eosinophilic inflammation induced by the intratracheally administered Ag. This inhibition reflected the mechanism of active suppression, since the inhibitory effect was adoptively transferred by splenic CD4+ T cells from the transgenic mice fed with high doses of **OVA**. The Ag specificity of the suppressor T cells was documented by the failure of spleen cells from mice that were orally tolerant of **OVA** to suppress irrelevant Ag, KLH-specific airway eosinophilic inflammation. The suppressive effect of the transferred T cells on eosinophil recruitment was neutralized by anti-TGF-beta mAb, but not anti-IFN-gamma mAb, indicating that the suppression is due to the inhibitory effect by secreted TGF-beta, but not to the dominance of the transferred Th1 cells over Th2 cells. This is the first study to reveal a link between **oral tolerance** and the regulation of Th2-mediated experimental tracheal eosinophilia through TGF-beta. Our experimental model suggests possible therapeutic applications of **oral tolerance** for the treatment of allergic disorders such as bronchial asthma.

L36 ANSWER 33 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
97:918406 The Genuine Article (R) Number: YK493. TH2-polarized immunological memory to inhalant allergens in atopics is established during infancy and early childhood. Yabuhara A; Macaubas C; Prescott S L; Venaille T J; Holt B J; Habre W; Sly P D; Holt P G (Reprint). TVW TELETHON INST CHILD HLTH RES, POB 855, PERTH, WA 6872, AUSTRALIA (Reprint); TVW TELETHON INST CHILD HLTH RES, PERTH, WA 6872, AUSTRALIA. CLINICAL AND EXPERIMENTAL ALLERGY (NOV 1997) Vol. 27, No. 11, pp. 1261-1269. Publisher: BLACKWELL SCIENCE LTD. OSNEY MEAD, OXFORD, OXON, ENGLAND OX2 0EL. ISSN: 0954-7894. Pub. country: AUSTRALIA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background There is increasing evidence that the T-cell reactivity to environmental allergens underlying expression of allergic disease in adulthood, develops initially during childhood. However, there is little information available on the kinetics of these early responses, or on the patterns of cytokine production during this period.

Objective The purpose of this study was twofold: to obtain further information on the reported differences between responses to food versus inhalant allergens during early childhood, and to ascertain the age-range over which T-cell responses to inhalant allergens become polarized towards the TH2 cytokine profile, in potentially atopic children.

Methods in vitro cytokine responses to house dust mite (HDM) and egg (**OVA**) were assessed by semiquantitative RT-PCR in panels of 2- and 5-year-old children and adults; lymphoproliferative responses to **OVA** were subjected to epitope analysis.

Results At age 2 years IL-4/LL-5 responses to HDM grouped with positive atopic family history, and by age 5 years cytokine responses correlated strongly with individual SPT reactivity to HDM. In contrast, **OVA** responses were restricted to weak and transient IL-5 signals in the 2-year-old family history positive group. Lymphoproliferation assays performed in parallel indicate a log-scale greater postnatal expansion of T-cell reactivity to the inhalant allergen; preliminary epitope analysis of **OVA** responses indicate that the number of **OVA** epitopes recognised decrease during early childhood.

Conclusions Inhalant allergen-specific in vitro cytokine production associated with positive skin-prick test (SPT) reactions, one of the hallmarks of adult atopy, manifests in children at or before 5 years of age; additionally, cytokine responses in SPT negative 5 year olds are restricted to IFN gamma, as per normal adults. In contrast, T-cell responses to a typical food allergen appear to be deleted during early childhood.

L36 ANSWER 34 OF 42 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
96136576 EMBASE Document No.: 1996136576. The absence of gut flora, the doses of antigen ingested and aging affect the long-term peripheral tolerance induced by ovalbumin feeding in mice. Moreau M.-C.; Gaboriau-Routhiau V.. UEPSD, Batiment 440, INRA,78352 Jouy-en-Josas Cedex, France. Research in Immunology 147/1 (49-59) 1996.
ISSN: 0923-2494. CODEN: RIMME5. Pub. Country: France. Language: English. Summary Language: English; French.

AB Several factors have been shown to affect the induction of peripheral tolerance induced by the oral route, also called **oral tolerance**. In the present study, we explored factors that shorten the duration of the IgG and IgE-antibody unresponsiveness induced after ingestion of ovalbumin (**OVA**). Accordingly, we explored the effects of aging, the absence of gut flora, and ingestion of either one dose of 20 mg **OVA** or 5 doses of 1 mg **OVA** in young adult conventional (CV) mice and germ-free (GF) mice, and older CV mice. In young CV mice fed 20 mg **OVA**, IgG and IgE antibody unresponsiveness were still observed 2 to 3 months after feeding. In CV mice, neither aging nor 5 low doses of **OVA** prevented the induction of IgG and IgE antibody unresponsiveness but they reduced its

duration. In young GF mice given 20 mg **OVA**, IgG antibody unresponsiveness only lasted between 7 and 21 days after feeding, but IgE antibody unresponsiveness lasted much longer. We believe these findings should be taken into account in the treatment of autoimmune and allergic diseases, for cases requiring conditions of antigen ingestion suitable for lasting suppression of peripheral antibody responses. The animal models used here might be of interest for better understanding of the mechanisms involved in the long-term persistence of **oral tolerance**
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L36 ANSWER 35 OF 42 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

95177639 EMBASE Document No.: 1995177639. γδ T cells down-regulate primary IgE responses in rats to inhaled soluble protein antigens. McMenamin C.; McKersey M.; Kuhnlein P.; Hunig T.; Holt P.G.. Division of Cell Biology, Institute for Child Health Research, P. O. Box 855,West Perth, WA 6872, Australia. Journal of Immunology 154/9 (4390-4394) 1995.
ISSN: 0022-1767. CODEN: JOIMA3. Pub. Country: United States. Language: English. Summary Language: English.

AB The biologic role and repertoire of cells bearing the γδ T cell receptor has not been fully defined. However, their tropism for epithelial microenvironments is recognized and suggests an important role for these cells in immune defense at mucosal tissue surfaces. The study presented below utilizes an experimental model in which repeated exposure of Brown Norway rats to **OVA** by inhalation induces a state of Ag-specific, IgE isotype- specific 'tolerance' via immune deviation. This process seems similar to **oral tolerance** in the gut.
This form of tolerance was adoptively transferred to naive syngeneic recipients by i.p. injection of as few as 103 positively selected TCR-γδ+ cells from **OVA**-exposed rats. These TCR-γδ+ T-cells are demonstrated to produce high levels of INF-γ in response to **OVA** stimulation, and this provides a potential mechanism for the inhibition of Th2 cell proliferation, resulting in suppression of IgE production. The unique potency of these cells in selective suppression of IgE Ab production in response to natural 'mucosal' Ag exposure suggests a potentially important role in protection against primary allergic sensitization in vivo.

L36 ANSWER 36 OF 42 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

1996:26448 Document No.: PREV199698598583. Effects of diphenyl dimethyl dicarboxylate on **oral tolerance** to ovalbumin in mice.
Kim, Joung Hoon [Reprint author]; Ahn, Young Keun. Cent. Food Drug Safety, Wonkwang Univ., Iksan, Chunrabukdo, 570-749, South Korea. Journal of Toxicological Sciences, (1995) Vol. 20, No. 4, pp. 375-382.
CODEN: JTSCDR. ISSN: 0388-1350. Language: English.

AB The effects of diphenyl dimethyl dicarboxylate (PMC) on **oral tolerance** to ovalbumin (**OVA**) were investigated in C3H/HeN and BALB/c mice. Mice orally received 20 mg **OVA** or 2% starch solution were immunized 7 days later with an i.p. injection of 0.1 mg **OVA** in complete Freund's adjuvant (CFA). The effects of oral **OVA** and PMC on antibody production were assessed by ELISA of immunoglobulin (Ig) subclass level in serum collected 7 days after immunization. **Oral tolerance** was obtained enough on day 7 after immunization and was more effective in C3H strain than in BALB strain, associated mainly with decreases of anti-**OVA** IgG, IgG1, IgG2a and IgM levels. After oral **OVA**, oral administrations of PMC for 6 days significantly elevated anti-**OVA** IgG, IgG1, IgG2a and IgM levels in mice hyposensitized by the oral **OVA**. These findings indicate that PMC is an useful modulator of **oral tolerance** to **OVA** in these two strains.

L36 ANSWER 37 OF 42 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

95:586937 The Genuine Article (R) Number: RR540. CHEMICAL DENATURATION OF OVALBUMIN ABROGATES THE INDUCTION OF **ORAL TOLERANCE** OF SPECIFIC IGG ANTIBODY AND DTH RESPONSES IN MICE. PENG H J (Reprint); CHANG Z N; HAN S H; WON M H; HUANG B T. VET GEN HOSP, DEPT MED RES, 201 SHIH PAI RD, TAIPEI 11217, TAIWAN (Reprint); VET GEN HOSP, DEPT PEDIAT, TAIPEI, TAIWAN; NATL YANG MING UNIV, FAC MED TECHNOL, TAIPEI, TAIWAN; NATL YANG MING UNIV, INST MICROBIOL & IMMUNOL, TAIPEI, TAIWAN. SCANDINAVIAN JOURNAL OF IMMUNOLOGY (SEP 1995) Vol. 42, No. 3, pp. 297-304. ISSN: 0300-9475. Pub. country: TAIWAN. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have examined the effects of ingestion of chemically denatured ovalbumin (**OVA**) in mice. Both 8 M urea-denatured **OVA** (UD-**OVA**) and carboxymethylated UD-**OVA** (CM-**OVA**) were purified by gel filtration. Specific IgG antibody and systemic delayed-type hypersensitivity (DTH) responses to **OVA** were not suppressed by CM-**OVA** fed prior to or after immunization with **OVA** in complete Freund's adjuvant (CFA). When CM-**OVA** was used instead of **OVA** for immunization, serum IgG and DTH responses to CM-**OVA** were or-ally tolerized by **OVA**, but not by UD-**OVA** or CM-**OVA**. Studies of antigen uptake in mice using sandwich ELISA tests showed that **OVA**, but not CM-**OVA**, was absorbed after antigen ingestion. In vitro studies further demonstrated that CM-**OVA** was digested much more rapidly than **OVA**. Moreover, studies using bovine serum albumin (BSA) demonstrated that both IgG and DTH responses to BSA were orally tolerant to BSA, but not to denatured BSA. Finally, studies using human gamma-globulin (HGG), a well-known tolerogen, also found that the IgG antibody response to HGG was not orally tolerized by denatured HGG. These results suggest that complete denaturation of globular proteins may affect their processing and absorption in the gut and thus abrogates **oral tolerance** induction.

L36 ANSWER 38 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

1994:407954 Document No. 121:7954 The effect of delayed weaning on the development of **oral tolerance** to soybean protein in pigs. Miller, B. G.; Whittemore, C. T.; Stokes, C. R.; Telemo, E. (Sch. Vet. Sci., Bristol Univ., Bristol, BS18 7DU, UK). British Journal of Nutrition, 71(4), 615-25 (English) 1994. CODEN: BJNUAV. ISSN: 0007-1145.

AB The antibody response to dietary antigen (soybean protein) and the development of **oral tolerance** was studied in pigs in a family pen system where the piglets are left with mothers and gradually wean themselves onto a soybean-based diet over a 12 wk period. In the first experiment three groups of pigs (eight pigs/group) aged either 2, 8 or 13 wk were immunized with soybean protein or ovalbumin (**OvA**; control) i.p. in Quill A adjuvant and subsequently boosted 2 wk later. All groups showed an IgG response to the injected antigens indicating lack of tolerance induction to the dietary antigen. Interestingly the groups injected with **OvA** showed an almost identical response to soybean protein as the groups injected with soybean protein. In a second experiment with a similar protocol, soybean was withdrawn from the feed before immunization which resulted in lack of response to soybean protein in the groups injected with **OvA** and a lack of response to injected soybean protein in the 14-wk-old group, indicating that systemic tolerance was established by 12 wk of age. The results from the two expts. suggest a compartmentalized response to soybean protein, i.e. local antibody production to dietary soybean along with systemic tolerance to injected soybean protein. The work also suggests that delayed 'natural' weaning may avoid damaging hypersensitivity reactions associated with early weaning.

L36 ANSWER 39 OF 42 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

88156531 EMBASE Document No.: 1988156531. Genetic control of oral to ovalbumin in mice. Lamont A.G.; Mowat McI. A.; Browning M.J.; Parrott

M.V.. Department of Bacteriology and Immunology, Western Infirmary, Glasgow G11 6NT, United Kingdom. Immunology 63/4 (737-739) 1988. ISSN: 0019-2805. CODEN: IMMUAM. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB We have investigated the genetic basis of **oral tolerance** to **OVA** in a number of inbred mouse strains. Our results emphasise the efficiency of the oral route for inducing tolerance and provide evidence for both MHC and non-MHC linked control of **oral tolerance**.

L36 ANSWER 40 OF 42 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

1986:126125 Document No.: PREV198681036541; BA81:36541. THE ROLE OF ANTIGEN RECOGNITION AND SUPPRESSOR CELLS IN MICE WITH **ORAL TOLERANCE** TO OVALBUMIN. MOWAT A M [Reprint author]. DEP BACTERIOL IMMUNOL, WESTERN INFIRMARY, GLASGOW G11 6NT, UK. Immunology, (1985) Vol. 56, No. 2, pp. 253-260.
CODEN: IMMUAM. ISSN: 0019-2805. Language: ENGLISH.

AB The induction of tolerance by feeding proteins may prevent potentially harmful delayed-type hypersensitivity (DTH) reactions to food antigens. Suppressor T cells (Ts) are present in mice with tolerance of systemic DTH after feeding ovalbumin (**OVA**) but, as other immunoregulatory mechanisms have also been described, the exact role of Ts in maintaining tolerance is not known. In this study, we have used the ability of native and denaturated **OVA** to cross-react at the level of helper/effector T cells, but not Ts, to re-examine the role of Ts in **oral tolerance** to **OVA**. Mice immunized with native **OVA** (nOVA) or denatured **OVA** (dOVA) in adjuvant had fully crossreacting DTH to either nOVA or dOVA, but intravenous administration of antigen induced Ts which were specific for the appropriate form. Mice fed nOVA or dOVA had identical tolerance of systemic DTH to both forms of **OVA**, and feeding nOVA induced splenic Ts which suppressed the DTH response to both nOVA and dOVA. Splenic Ts could not be detected in mice fed dOVA. The results support the hypothesis that tolerance of systemic DTH in mice fed native proteins is due to Ts. Although, for the moment, there is no complementary evidence for a role for Ts in **oral tolerance** to denatured proteins, this study is consistent with the idea that Ts are the mechanism which normally prevent enteropathy due to DTH against dietary proteins. In addition, our study underlines the differences between orally and parenterally induced Ts and reinforces the view that fed proteins induce Ts and reinforces the view that fed proteins induce Ts after processing by the gut or its lymphoid accessory cells.

L36 ANSWER 41 OF 42 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

84021845 EMBASE Document No.: 1984021845. Immunological responses to fed protein antigens in mice. IV. Effects of stimulating the reticuloendothelial system on **oral tolerance** and intestinal immunity to ovalbumin. Mowat McI. A.; Parrot D.M.V.. Department of Bacteriology and Immunology, University of Glasgow, Glasgow, United Kingdom. Immunology 50/4 (547-554) 1983.
CODEN: IMMUAM. Pub. Country: United Kingdom. Language: English.

AB We have studied the role of the reticuloendothelial system (RES) in intestinal and systemic immunity in mice immunized orally with ovalbumin (**OVA**). Stimulation of the RES by oestradiol completely prevented the induction of systemic tolerance normally found in mice fed 25 mg **OVA** and this applied both to humoral immunity and delayed-type hypersensitivity (DTH). In addition, an active DTH response could be detected in the mucosa and mesenteric lymph nodes (MN) of oestradiol-treated, **OVA**-fed mice on oral challange with **OVA**. Oestradiol had no direct effect on lymphocyte function and we propose that RES activation may be one mechanism which predisposes to small intestinal disease associated with food hypersensitivity.

L36 ANSWER 42 OF 42 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
1981:295998 Document No.: PREV198172080982; BA72:80982. ORALLY INDUCED TOLERANCE DEFINITION AT THE CELLULAR LEVEL. TITUS R G [Reprint author]; CHILLER J M. NATL JEW HOSP RES CENT, 3800 EAST COLFAX AVE, DENVER, COLO 80206, USA. International Archives of Allergy and Applied Immunology, (1981) Vol. 65, No. 3, pp. 323-338.
CODEN: IAAAAM. ISSN: 0020-5915. Language: ENGLISH.

AB Several elements of the phenomenon of **oral tolerance** were examined. Intragastric (i.g.) exposure of mice to the T-dependent antigens ovalbumin (**OVA**), bovine serum albumin and human γ globulin severely compromised the ability to respond to a subsequent challenge with the homologous antigen; i.g. treatment with T-independent antigens such as dinitrophenylated Ficoll, polyvinylpyrrolidone and bacterial [Escherichia coli] lipopolysaccharide (LPS) did not induce anergy. Mice parenterally primed to **OVA** were not only refractory to **oral tolerance** induction with **OVA**, but displayed an anamnestic response following i.g. treatment with the antigen. Mice administered **OVA** orally lost specific T cell functions such as the ability to provide helper activity, to proliferate in response to antigen and to mediate delayed-type hypersensitivity. Such animals possessed **OVA**-specific functional B cells as evidenced by the capacity to respond to **OVA** when the antigen was administered, either linked to a recognizable carrier or in conjunction with LPS.

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(FILE 'HOME' ENTERED AT 17:24:55 ON 13 APR 2004)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 17:25:06 ON 13 APR 2004

L1	7779567	S	TREATMENT
L2	39386	S	L1 AND ALLERGY
L3	10	S	L2 AND CHOLERA TOXIN B SUBUNIT
L4	6	DUP	REMOVE L3 (4 DUPLICATES REMOVED)
L5	0	S	L2 AND MUCOSAL ADJUDVANT
L6	0	S	L2 AND E COLI ENTEROTOXIN B SUBUNIT
L7	0	S	L2 AND "ETX"
L8	0	S	L2 AND "ETXB"
L9	0	S	L2 AND E COLI HEAT LABEL ENTEROTOXIN
L10	32	S	L2 AND ENTEROTOXIN
L11	30	DUP	REMOVE L10 (2 DUPLICATES REMOVED)
L12	1480	S	L2 AND TOLERANCE
L13	0	S	L12 AND "CTXB"
L14	411	S	"CTXB"
L15	0	S	L14 AND TYPE I ALLERGY
L16	1	S	L14 AND ALLERGY
L17	2899736	S	COMPOSITION
L18	2213	S	L17 AND ALLERGEN
L19	0	S	L18 AND UNCONJUGATE
L20	53	S	L18 AND TYPE I
L21	0	S	L20 AND MUCOSA BINDING AGENT
L22	0	S	MUCOSA BINDING AGENT
L23	104	S	GM1 GANGLIOSIDE RECEPTOR
L24	0	S	L23 AND BINDING AGENT
L25	4942	S	ORAL TOLERANCE
L26	614	S	L25 AND ALLERGY
L27	8	S	L26 AND CHOLERA TOXIN B SUBUNIT
L28	4	DUP	REMOVE L27 (4 DUPLICATES REMOVED)
L29	34	S	L26 AND CHOLERA TOXIN
L30	18	DUP	REMOVE L29 (16 DUPLICATES REMOVED)

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L31             2 S L26 AND ENTEROTOXIN
L32             2 DUP REMOVE L31 (0 DUPLICATES REMOVED)
L33             0 S L26 AND COADMINISTERED
L34           361 DUP REMOVE L26 (253 DUPLICATES REMOVED)
L35            42 S L34 AND OVA
L36            42 DUP REMOVE L35 (0 DUPLICATES REMOVED)

=> s l34 and asthma
L37           28 L34 AND ASTHMA

=> dup remove l37
PROCESSING COMPLETED FOR L37
L38            28 DUP REMOVE L37 (0 DUPLICATES REMOVED)

=> d l38 1-28 cbib abs

L38  ANSWER 1 OF 28      MEDLINE on STN
2004117631.    PubMed ID: 15007630.   Effects of intestinal microflora and the
     environment on the development of asthma and allergy.
     Bjorksten Bengt. (Centre for Allergy Research and Department of
     Environmental Medicine, Karolinska Institutet, 171 77 Stockholm, Sweden..
     bengt.bjorksten@cfa.ki.se) . Springer seminars in immunopathology, (2004
     Feb) 25 (3-4) 257-70.  Journal code: 7910384. ISSN: 0344-4325. Pub.
     country: Germany: Germany, Federal Republic of. Language: English.
AB   The aim of previous research into the causes of allergic diseases,
     including asthma was mostly to identify potential risk factors
     in the environment.  No major risk factors have been identified, however.
     Over the past 10 years, focus has, therefore, more been directed towards
     protective factors that could enhance the development of tolerance to
     allergens which were previously encountered early in life, but are now
     lost in modern affluent societies.  In particular, the role of childhood
     infections has been discussed, but so far these studies have not been
     conclusive.  Recent epidemiological studies and experimental research
     suggest that the microbial environment and exposure to microbial products
     in infancy modifies immune responses and enhances the development of
     tolerance to ubiquitous allergens.  The intestinal microflora may play a
     particular role in this respect, as it is the major external driving force
     in the maturation of the immune system after birth, and animal experiments
     have shown it to be a prerequisite for normal development of oral
     tolerance.  Recent studies have shown differences in the
     composition of the microflora between healthy and allergic infants in
     countries with a high and low prevalence of allergies and
     between healthy and allergic infants within such countries.  These
     differences are apparent within the first week of life and thus precede
     clinical symptoms.  The use of live microorganisms that might be
     beneficial to health has a long tradition and the safety is well
     documented.  Very recently, several prospective intervention studies,
     modifying the gut flora from birth have yielded encouraging results and
     may suggest a new mode of primary prevention of allergy in the
     future.

L38  ANSWER 2 OF 28  BIOSIS  COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2004:186495  Document No.: PREV200400186627. An experimental animal model for
     investigation of the influence of oral tolerance on
     airway hyperreactivity. Nakonechna, A. [Reprint Author]; Renz, H.;
     Wegmann, M.; Drannik, G. [Reprint Author]; Dubuske, L. M.. National
     Medical University, Kiev, Ukraine. Journal of Allergy and Clinical
     Immunology, (February 2004) Vol. 113, No. 2 Supplement, pp. S105. print.
     Meeting Info.: 60th Annual Meeting of the American Academy of Allergy,
     Asthma and Immunology (AAAAI). San Francisco, CA, USA. March 19-23, 2004.
     American Academy of Allergy, Asthma and Immunology.
     CODEN: JACIBY. ISSN: 0091-6749. Language: English.
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L38 ANSWER 3 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2004:114389 The Genuine Article (R) Number: 766VY. Clinical efficacy of microencapsulated Timothy grass pollen extract in grass-allergic individuals. TePas E C (Reprint); Hoyte E G; McIntire J J; Umetsu D T. Massachusetts Gen Hosp, 15 Parkman St ACC 712, Boston, MA 02114 USA (Reprint); Stanford Univ, Dept Pediat, Div Immunol & Allergy, Stanford, CA 94305 USA. ANNALS OF ALLERGY ASTHMA & IMMUNOLOGY (JAN 2004) Vol. 92, No. 1, pp. 25-31. Publisher: AMER COLL ALLERGY ASTHMA IMMUNOLOGY. 85 WEST ALGONQUIN RD SUITE 550, ARLINGTON HTS, IL 60005 USA. ISSN: 1081-1206. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Conventional allergen immunotherapy is clinically effective in reducing the symptoms of allergic rhinitis and **asthma**. It differs from other pharmacotherapies in that it can induce long-term clinical remission of these diseases. However, it requires years of treatment and is associated with serious allergic reactions.

Objective: To evaluate the safety, clinical efficacy, and immunologic mechanisms of immunotherapy with an oral, microencapsulated form of timothy grass allergen.

Methods: In this double-blind, placebo-controlled study, 24 patients aged 19 to 55 years with grass pollen **allergy** were randomized to receive either microencapsulated timothy grass pollen extract or placebo once a day for 10 weeks. The dose of study drug was doubled weekly. Safety was evaluated through weekly visits, daily symptom diaries, and routine laboratory tests. Efficacy was evaluated by comparing medication use and symptoms scores during peak grass pollen season before and after treatment. Allergen-specific T-cell responses, cytokine production, and IgG, IgE, and skin reactivity were measured to evaluate immunologic mechanisms.

Results: Eleven of 12 patients in the active treatment group had a decrease in the combined medication and symptom score, but only 4 of 10 patients in the placebo group had a decrease in scores. The proliferative response to timothy grass was reduced by at least 30% in 9 of the 12 grass-treated patients, but only 3 of 11 placebo patients had a proliferative response reduction. Timothy grass-induced interieukin-5 messenger RNA was reduced in the active group, but not in the placebo group. There were no significant changes in either group in IgG, IgE, and skin reactivity.

Conclusions: Oral immunotherapy with microencapsulated allergen induces a(.)form of immunologic tolerance to the allergen and is a safe, efficient, and effective method of allergen immunotherapy.

L38 ANSWER 4 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:719417 The Genuine Article (R) Number: 710EG. A plant-based **allergy** vaccine suppresses experimental **asthma** via an IFN-gamma and CD4(+) CD45RB(low) T cell-dependent mechanism. Smart V; Foster P S; Rothenberg M E; Higgins T J V; Hogan S P (Reprint). Australian Natl Univ, John Curtin Sch Med Res, Div Mol Biol & Biochem, Allergy & Inflammat Res Grp, GPO Box 4, Canberra, ACT 0200, Australia (Reprint); Australian Natl Univ, John Curtin Sch Med Res, Div Mol Biol & Biochem, Allergy & Inflammat Res Grp, Canberra, ACT 0200, Australia; Childrens Hosp, Ctr Med, Div Allergy & Immunol, Cincinnati, OH 45229 USA; PlantImmunex Diagnost, Canberra, ACT, Australia; Commonwealth Sci & Ind Res Org Plant Ind, Canberra, ACT, Australia. JOURNAL OF IMMUNOLOGY (15 AUG 2003) Vol. 171, No. 4, pp. 2116-2126. Publisher: AMER ASSOC IMMUNOLOGISTS. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA. ISSN: 0022-1767. Pub. country: Australia; USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Allergic **asthma** is currently considered a chronic airway inflammatory disorder associated with the presence of activated CD4(+) Th2-type lymphocytes, eosinophils, and mast cells. Interestingly, therapeutic strategies based on immune deviation and suppression have been shown to successfully attenuate the development of the **asthma**

phenotype. In this investigation, we have for the first time used a genetically modified (GM) plant, narrow leaf lupin (Lupinus angustifolius L.), expressing a gene for a potential allergen (sunflower seed albumin) (SSA-lupin) to examine whether a GM plant/food-based vaccine strategy can be used to suppress the development of experimental **asthma**. We show that oral consumption of SSA-lupin promoted the induction of an Ag-specific IgG2a Ab response. Furthermore, we demonstrate that the plant-based vaccine attenuated the induction of delayed-type hypersensitivity responses and pathological features of experimental **asthma** (mucus hypersecretion, eosinophilic inflammation, and enhanced bronchial reactivity (airways hyperreactivity). The suppression of experimental **asthma** by SSA-lupin was associated with the production of CD4(+) T cell-derived IFN-gamma and IL-10. Furthermore, we show that the specific inhibition of experimental **asthma** was mediated via CD4(+)CD45RB(low) regulatory T cells and IFN-gamma. Thus, our data demonstrate that a GM plant-based vaccine can promote a protective immune response and attenuate experimental **asthma**, suggesting that plant-based vaccines may be potentially therapeutic for the protection against allergic diseases.

L38 ANSWER 5 OF 28 MEDLINE on STN

2003221489. PubMed ID: 12743572. Oral administration of specific antigens to **allergy**-prone infant dogs induces IL-10 and TGF-beta expression and prevents **allergy** in adult life. Zemann Barbara; Schwaerzler Christoph; Griot-Wenk Monika; Nefzger Marijke; Mayer Peter; Schneider Heinz; de Weck Alain; Carballido Jose M; Liehl Ekke. (Novartis Research Institute, Vienna, Austria.) Journal of allergy and clinical immunology, (2003 May) 111 (5) 1069-75. Journal code: 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.

AB BACKGROUND: Oral administration of allergens can induce immune tolerance to specific allergens in rodents and hence might be a possibility to prevent and treat allergic diseases in human subjects. However, the gastrointestinal tract of mice is different from that of human subjects. The absorption of specific antigens and subsequent antigen presentation to intestinal T cells is different in both species, making it difficult to extrapolate results. OBJECTIVE: We investigated primary **oral tolerance** to ovalbumin (OVA) in an IgE high-responder dog model, which is more predictive for human allergic diseases than corresponding rodent models. METHODS: **Oral tolerance** was induced by means of a 28-day treatment with OVA dissolved in cow's milk. RESULTS: We observed reduced OVA-specific IgE and IgG production in response to ensuing subcutaneous challenges. Allergic conjunctivitis induced by means of ocular and airway provocation was significantly reduced in tolerized animals compared with that seen in nontolerized control animals. In addition, eosinophilia and neutrophilia in bronchoalveolar lavage fluid and bronchoconstriction after airway allergen challenge were significantly suppressed in tolerized animals. Cytokine analysis by means of real-time PCR on bronchoalveloar fluid cells after allergen challenge revealed a high-level expression of IL-10 and transforming growth factor beta, predominantly in the CD14(+) population. CONCLUSION: Feeding infant beagles with OVA for 4 weeks is sufficient to prevent hallmark manifestations of **asthma** and **allergy** in adult life. The mechanism of **oral tolerance** involved an increased expression of IL-10 and transforming growth factor beta cytokines.

L38 ANSWER 6 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2003:300973 The Genuine Article (R) Number: 661NU. Breast milk fatty acids, eicosanoids, and cytokines in mothers with and without allergic disease. Laiho K (Reprint); Lampi A M; Hamalainen M; Moilanen E; Piironen V; Arvola T; Syrjanen S; Isolauri E. Univ Turku, Dept Pediat, POB 52, Turku 20521, Finland (Reprint); Univ Turku, Dept Paediat, Turku 20521, Finland; Univ Turku, Inst Dent, Turku 20521, Finland; Univ Helsinki, Dept Appl Chem & Microbiol, Helsinki, Finland; Univ Tampere, Immunopharmacol Res Grp, Sch

Med, FIN-33101 Tampere, Finland; Univ Tampere, Dept Pediat, FIN-33101 Tampere, Finland; Tampere Univ Hosp, Tampere, Finland. PEDIATRIC RESEARCH (APR 2003) Vol. 53, No. 4, pp. 642-647. Publisher: INT PEDIATRIC RESEARCH FOUNDATION, INC. 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436 USA. ISSN: 0031-3998. Pub. country: Finland. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Allergic disease (AD), including atopic eczema, **asthma**, allergic rhinitis, and food **allergy**, is characterized by an imbalance between cytokines produced by distinct T-helper cell subtypes. Whether this imbalance can be transferred from mother to breast milk remains to be established. The objective was to investigate the concentrations and interactions of nutritional and inflammatory factors in breast milk. Breast milk samples were collected from mothers with AD (n = 43) and without AD (n = 51). The concentrations of transforming growth factor (TGF)-beta(2), tumor necrosis factor-alpha, IL-4, IL-10, prostaglandin E-2 and cysteinyl leukotrienes were measured by immunoassays and fatty acid composition by gas chromatography. Mothers with AD had a lower concentration of TGF-beta(2) in breast milk [median (interquartile range), 420 (278-701) ng/L] compared with those without AD [539 (378-1108) ng/L; p = 0.003], whereas other cytokines, prostaglandin E-2, and cysteinyl leukotriene concentrations or fatty acid composition were not significantly different between the groups. The breast milk inflammatory factors and fatty acid composition were shown to be related. A positive association was observed between TGF-beta(2) and the proportion of polyunsaturated fatty acids (p = 0.038) and a negative association between TGF-beta(2) and the proportion of saturated fatty acids (p = 0.029) in breast milk. The reduced TGF-beta(2) concentration in the breast milk of mothers with AD may interfere with the development of the mucosal immune system of the breast-fed infant. The observed associations between nutritional and inflammatory factors in breast milk suggest that it may be possible to influence the immunologic properties of breast milk by dietary intervention of the mother.

L38 ANSWER 7 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:1069032 The Genuine Article (R) Number: 748LB. Role of regulatory T cells in **allergy** and **asthma**. Akbari O (Reprint); Stock P; DeKruyff R H; Umetsu D T. Stanford Univ, Dept Pediat, Div Immunol & Allergy, Stanford, CA 94305 USA (Reprint). CURRENT OPINION IN IMMUNOLOGY (DEC 2003) Vol. 15, No. 6, pp. 627-633. Publisher: CURRENT BIOLOGY LTD. 84 THEOBALDS RD, LONDON WC1X 8RR, ENGLAND. ISSN: 0952-7915. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Th2 cells play a critical role in the pathogenesis of **allergy** and **asthma**. However, the immunological mechanisms that downmodulate and protect against the development of these disorders are poorly understood. A spectrum of CD4(+) T cells, including Th3 cells, T-R cells, CD4(+)CD25(+) cells and NKT cells play a critical role in regulating these diseases. A better understanding of the role of regulatory cells in allergic diseases may lead to the identification of novel therapeutic targets.

L38 ANSWER 8 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:803232 The Genuine Article (R) Number: 719XW. Regulatory T cells control the development of allergic disease and **asthma**. Umetsu D T (Reprint); Akbari O; DeKruyff R H. Stanford Univ, Dept Pediat, Div Immunol & Allergy, Rm G309, Stanford, CA 94305 USA (Reprint); Stanford Univ, Dept Pediat, Div Immunol & Allergy, Stanford, CA 94305 USA. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (SEP 2003) Vol. 112, No. 3, pp. 480-487. Publisher: MOSBY, INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318 USA. ISSN: 0091-6749. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The role of T(H)2 cells in the pathogenesis of **allergy** and **asthma** has been well described. However, the immunologic

mechanisms that downmodulate and protect against the development of these disorders are poorly characterized. A spectrum of CD4(+) T cells, including T(H)1 cells, T(H)3 cells, regulatory T cells, CD25(+) T cells, and natural killer T cells might play a critical role in regulating these diseases and are discussed in this review.

L38 ANSWER 9 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:477629 The Genuine Article (R) Number: 684LN. Further evidence regarding the effect of dietary protein on **oral tolerance** against beta-lactoglobulin through Th1-mediated immune response in mice. Ahmed S; Satter M A; Yamamoto S; Maeda K; Minato Y; Ota F (Reprint). Univ Tokushima, Dept Food Microbiol, Tokushima 7708503, Japan (Reprint); Univ Tokushima, Hlth Serv Ctr, Tokushima 7708503, Japan; Univ Tokushima, Fac Med, Sch Nutr, Dept Appl Nutr, Tokushima 7708503, Japan. JOURNAL OF NUTRITIONAL SCIENCE AND VITAMINOLOGY (APR 2003) Vol. 49, No. 2, pp. 112-119. Publisher: CENTER ACADEMIC PUBL JAPAN. 2-4-16 YAYOI, BUNKYO-KU, TOKYO, 113-0032, JAPAN. ISSN: 0301-4800. Pub. country: Japan. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Oral tolerance** is a potential strategy for preventing or minimizing aberrant immune responses. Although, **oral tolerance** has been extensively studied, to date the effects of dietary protein on the induction of **oral tolerance** are poorly understood. We have previously shown that restricted dietary protein induces **oral tolerance** to ovalbumin. This study was designed to investigate whether or not such tolerance occurs with beta-lactoglobulin (BLG) instead of ovalbumin (OVA) and if the tolerance resulting from this feeding regimen involves Th1-mediated immune response. Female BALB/c mice fed either 20% or 5% dietary protein were given 5 mg BLG or water orally for four consecutive days and then immunized intraperitoneally (ip) twice with BLG at 3-wk intervals. **Oral tolerance** induction was compared in BLG-fed and water-fed mice by measuring total IgE, BLG-specific antibodies, footpad reactions, splenocyte proliferation, and cytokine production. When mice were given BLG orally before ip immunization, the Th1-mediated immune responses (production of IL-2, IFN-gamma, and IgG2a) were significantly reduced, whereas the Th2-mediated immune responses (production of IL-4 and IgG1) were unchanged. The Th1-mediated immune responses were markedly down-regulated in mice fed 5% protein as compared to those in mice fed 20%, protein. Moreover, the production of total IgE, BLG-specific IgE, splenocyte proliferation, and footpad reactions were more reduced in mice fed 5% protein than those in mice fed 20%,, protein. The present study provides evidence that dietary protein plays an important role in the induction of **oral tolerance** against BLG as the result of, clear down-regulation of Th1 helper activity accompanied by a reduction in IgE.

L38 ANSWER 10 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:547537 The Genuine Article (R) Number: 693FP. Breast-feeding, infant formulas, and the immune system. Hanson L A (Reprint); Korotkova M; Telemo E. Guldhedsgatan 10, S-41346 Gothenburg, Sweden (Reprint); Univ Gothenburg, Dept Clin Immunol, Gothenburg, Sweden; Univ Gothenburg, Dept Pediat, Gothenburg, Sweden. ANNALS OF ALLERGY ASTHMA & IMMUNOLOGY (JUN 2003) Vol. 90, No. 6, Supp. [3], pp. 59-63. Publisher: AMER COLL ALLERGY ASTHMA IMMUNOLOGY. 85 WEST ALGONQUIN RD SUITE 550, ARLINGTON HTS, IL 60005 USA. ISSN: 1081-1206. Pub. country: Sweden. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective: Breast-feeding provides many advantages to the offspring, but presently there is an ongoing debate whether or not it prevents **allergy** any better than certain formulas. This report reviews the mechanisms involved and discusses how breast-feeding may protect against **allergy**.
Data Sources: The review builds on an internet-based literature search

in addition to our own data.

Results: Human milk is the food best adapted to the needs of the offspring, also because it provides efficient protection against infections and actively stimulates the development of the infant's own immune system. The major host defense system is provided via the secretory IgA antibodies produced in the mammary glands by lymphocytes, which have migrated there from the mother's gut mucosa. Therefore, these antibodies in the milk are primarily directed against the microbes in the mother's gut and her food proteins. As a result, breast-feeding starting directly after delivery will provide an excellent defense against the microbes normally meeting the neonate and needed to induce development of its immune system. The milk also contains numerous components, which seem to enhance the infant's host defense as well as capacity to develop tolerance, helping to avoiding allergic reactivity to foods, etc.

Conclusions: Several studies show that breast-feeding prevents allergic diseases, but there are also good disagreeing studies. Supported by animal data, it seems that protection is enhanced in areas with more advantageous fat intake, inter alia lower ratio of n-6/n-3 fatty acids. Breast-feeding seems to protect against future development of allergic diseases, but possibly less so in countries with an untoward maternal fat intake.

L38 ANSWER 11 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2002:477080 The Genuine Article (R) Number: 557MJ. Critical role of B cells in the development of T cell tolerance to aeroallergens. Tsitoura D C; Yeung V P; DeKruyff R H; Umetsu D T (Reprint). Stanford Univ, Dept Pediat, Div Immunol & Allergy, Stanford, CA 94305 USA (Reprint). INTERNATIONAL IMMUNOLOGY (JUN 2002) Vol. 14, No. 6, pp. 659-667. Publisher: OXFORD UNIV PRESS. GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND. ISSN: 0953-8178. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Respiratory exposure to allergen induces the development of allergen-specific CD4(+) T cell tolerance that effectively protects against the development of allergic-sensitization and T(h)2-biased immunity. The establishment of T cell unresponsiveness to aeroallergens is an active process preceded by a transient phase of T cell activation that requires T cell co-stimulation and is critically influenced by the antigen-presenting cell type. In this study we examined the role of B cells in the development of respiratory tolerance following intranasal (i.n.) exposure to a prototypic protein antigen. We found that respiratory exposure of BCR-transgenic (Tg) mice to minute quantities of cognate antigen effectively induced T cell unresponsiveness, indicating that antigen presentation by antigen-specific B cells greatly enhanced the development of respiratory tolerance. In contrast, respiratory T cell unresponsiveness could not be induced in B cell-deficient JHD mice exposed to i.n. antigen, although T cell tolerance developed in JHD mice reconstituted with B cells, suggesting that B cells are required for the induction of respiratory T cell tolerance. Respiratory exposure of BCR-Tg mice to cognate antigen induced activation of antigen-specific T cells and partial activation of antigen-specific B cells, as demonstrated by enhanced expression by B cells of class II MHC and B7 molecules but lack of antibody secretion. Our data indicate that B cells critically influence the immune response to inhaled allergens and are required for the development of allergen-specific T cell unresponsiveness induced by respiratory allergen.

L38 ANSWER 12 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2002:334029 The Genuine Article (R) Number: 541QB. Inhalation of a harmless antigen (ovalbumin) elicits immune activation but divergent immunoglobulin and cytokine activities in mice. Swirski F K; Gajewska B U; Alvarez D; Ritz S A; Cundall M J; Cates E C; Coyle A J; Gutierrez-Ramos J C; Inman M D; Jordana M; Stampfli M R (Reprint). McMaster Univ, Dept Pathol & Mol Med, Hlth Sci Ctr, Div Resp Dis, Room 4H21A, 1200 Main St W, Hamilton, ON L8N 3Z5, Canada (Reprint); McMaster Univ, Dept Pathol & Mol Med, Hlth Sci

Ctr, Div Resp Dis, Hamilton, ON L8N 3Z5, Canada; McMaster Univ, Ctr Gene Therapeut, Hamilton, ON L8N 3Z5, Canada; Millennium Pharmceut, Cambridge, MA USA; McMaster Univ, Dept Med, Hamilton, ON L8N 3Z5, Canada. CLINICAL AND EXPERIMENTAL ALLERGY (MAR 2002) Vol. 32, No. 3, pp. 411-421. Publisher: BLACKWELL PUBLISHING LTD. P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND. ISSN: 0954-7894. Pub. country: Canada; USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background Exposure to aerosolized harmless antigen such as ovalbumin (OVA) has previously been shown to induce inhalation tolerance, a state characterized by inhibition of IgE synthesis and airway inflammation, upon secondary immunogenic antigen encounter. Immune events associated with this phenomenon are still poorly understood.

Objective The aim of this study was to investigate cellular and molecular mechanisms underlying this state of 'unresponsiveness'.

Methods; After initial repeated OVA exposure, mice were subjected to a protocol of antigen-induced airway inflammation, encompassing two intraperitoneal injections of OVA adsorbed to aluminium hydroxide followed by airway challenge. We assessed immune events in the draining lymph nodes after sensitization, and in the lungs after challenge.

Results In animals initially exposed to OVA, we observed, at the time of sensitization, considerable expansion of T cells, many of which expressed the activation markers CD69 and CD25, as well as increased numbers of antigen-presenting cells, particularly B cells. While these animals produced low levels of IgE, the observed elevated levels of IgG1 signified isotype switching. Splenocytes and lymph node cells from OVA-exposed mice produced low levels of IL-4, IL-5, IL-13 and IFN-gamma, indicating aborted effector function of both T helper (Th)2- and Th1-associated cytokines. Real time quantitative polymerase chain reaction (PCR) (TaqMan) analysis of costimulatory molecules in the lungs after in vivo challenge showed that B7.1, B7.2, CD28 and CTLA-4 mRNA expression was low in animals initially exposed to OVA. Ultimately, these events were associated with abrogated airway inflammation and attenuated airway hyper-responsiveness. The decreased inflammation was antigen-specific and independent of IL-10 or IFN-gamma.

Conclusion Initial exposure to OVA establishes a programme that prevents the generation of intact, fully functional inflammatory responses upon secondary antigen encounter. The absence of inflammation, however, is not associated with categorical immune unresponsiveness.

L38 ANSWER 13 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2002:927109 The Genuine Article (R) Number: 613RE. Atopic and nonatopic IgE-mediated **allergy**: A new interpretation of old facts?. de Weck A L (Reprint). Univ Fribourg, Beaumont 18, CH-1700 Fribourg, Switzerland (Reprint); Gerimmun Fdn, Fribourg, Switzerland. INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY (OCT 2002) Vol. 129, No. 2, pp. 97-107. Publisher: KARGER. ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND. ISSN: 1018-2438. Pub. country: Switzerland. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Coined 80 years ago, the term 'atopy' to designate a group of diseases associated with IgE and a hereditary background has raised many discussions. In particular, it is difficult to consider as part of an atopic syndrome cases of IgE-mediated **allergies** to isolated allergens without evidence of a familial inheritance. The postulate expressed in this essay is that in humans we are essentially dealing with an atopic IgE-mediated **allergy**, which is the equivalent of a genetically determined high IgE response, and with a nonatopic IgE-mediated **allergy**, which is the equivalent of a low IgE response in mammals and rodents. Copyright (C) 2002 S. Karger AG, Basel.

L38 ANSWER 14 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2002:198566 The Genuine Article (R) Number: 525GV. Mucosal tolerance as therapy of type I **allergy**: intranasal application of recombinant

Bet v 1, the major birch pollen allergen, leads to the suppression of allergic immune responses and airway inflammation in sensitized mice. Winkler B; Baier K; Wagner S; Repa A; Eichler H G; Scheiner O; Kraft D; Wiedermann U (Reprint). Univ Vienna, AKH, Dept Clin Pharmacol, Waehringer Guertel 18-20, A-1090 Vienna, Austria (Reprint); Univ Vienna, AKH, Dept Clin Pharmacol, A-1090 Vienna, Austria; Univ Vienna, Dept Pathophysiol, A-1090 Vienna, Austria. CLINICAL AND EXPERIMENTAL ALLERGY (JAN 2002) Vol. 32, No. 1, pp. 30-36. Publisher: BLACKWELL SCIENCE LTD. P O BOX 88, OSNEY MEAD, OXFORD OX2 0NE, OXON, ENGLAND. ISSN: 0954-7894. Pub. country: Austria. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background Several studies have demonstrated that mucosal administration of soluble antigens can prevent the onset or reduce the severity of certain autoimmune diseases or **allergies**. Few studies exist showing the efficacy of mucosal tolerance for therapy of such diseases.

Objective The aim of the present study was to modulate an allergic immune response by intranasal antigen administration in an already sensitized organism.

Methods A murine model of allergic **asthma** to birch pollen (BP) and its major allergen Bet v 1 was utilized. Sensitized mice were intranasally treated with recombinant (r)Bet v 1 in different concentrations and at different intervals. On the day the mice were killed, blood and bronchoalveolar lavage fluids were taken and immediate type I skin tests were performed. T cell proliferation and cytokine production (interleukin (IL)-5, interferon (IFN)-gamma) were measured in spleen and lung cell cultures.

Results Mucosal treatment with rBet v 1 (3 x 50 mug in 4 day intervals) led to a reduction of type I skin reactions, suppressed immunoglobulin (Ig)G I/IgE antibody levels and markedly decreased IL-5 and IFN-gamma production in vitro in spleen and lung cell cultures. Moreover, lung inflammation (i.e. eosinophilia and IL-5 levels in bronchoalveolar lavage fluids) was significantly suppressed by the treatment.

Conclusion Our results demonstrate that intranasal treatment with rBet v 1 reduced systemic allergic immune responses as well as air-way inflammation in BP-sensitized mice. We therefore suggest that mucosal tolerance induction with recombinant allergens could be a promising concept for the therapy of allergic diseases.

L38 ANSWER 15 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2002:851978 The Genuine Article (R) Number: 602MQ. Novel probiotics for the management of allergic inflammation. von der Weid T (Reprint); Ibnou-Zekri N; Pfeifer A. Nestle Res Ctr, POB 44, CH-1000 Lausanne 26, Switzerland (Reprint); Nestle Res Ctr, CH-1000 Lausanne 26, Switzerland. DIGESTIVE AND LIVER DISEASE (SEP 2002) Vol. 34, Supp. [2], pp. S25-S28. Publisher: PACINI EDITORE. VIA DELLA GHERARDESCA-ZONA INDUSTRIALE OSPEDALETTO, 56121 PISA, ITALY. ISSN: 1590-8658. Pub. country: Switzerland . Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Several pathologies of the gastrointestinal tract, particularly food **allergy**, are due to an exaggerated and imbalanced response of the gut mucosal immune system. The intestinal microflora is an important constituent of the gut mucosal barrier against food allergens and there is increasing evidence that one important acquired factor predisposing to food **allergy** in infants is the gut microflora. Indeed, the balance of bifidobacteria versus Clostridia In the neonatal flora appears to determine the allergic status In infants. In earlier studies, It was shown that the higher prevalence of **allergies** in infants fed standard formulas, compared to breast-fed infants, correlated with lower frequencies of bifidobacteria in their, faeces. Certain Lactobacillus probiotic strains can have an inhibitory impact on allergic inflammation. The mechanisms implicated are still unclear but it seems that they can involve both proteolytic and/or immunomodulatory functions. One challenge

will be to find a probiotic strain that elicits all these functions and that fulfills all safety criteria.

L38 ANSWER 16 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:719710 The Genuine Article (R) Number: 469HH. Consumption of hypoallergenic flour prevents gluten-induced airway inflammation in brown Norway rats. Watanabe J (Reprint); Tanabe S; Watanabe M; Kasai T; Sonoyama K. Hokkaido Univ, Grad Sch Agr, Sapporo, Hokkaido 0608589, Japan (Reprint); Japan Soc Promot Sci, Chiyoda Ku, Tokyo 1028471, Japan; Tokyo Gakugei Univ, Fac Educ, Koganei, Tokyo 1848501, Japan. BIOSCIENCE BIOTECHNOLOGY AND BIOCHEMISTRY (AUG 2001) Vol. 65, No. 8, pp. 1729-1735. Publisher: JAPAN SOC BIOSCI BIOTECHN AGROCHEM. JAPAN ACAD SOC CTR BLDG, 2-4-6 YAYOI BUNKYO-KU, TOKYO, 113, JAPAN. ISSN: 0916-8451. Pub. country: Japan. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Brown Norway rats were immunized with gluten, and then fed a diet containing hypoallergenic flour or an amino acid mixture. The rats were then made to inhale a solubilized gluten to induce gluten-specific bronchial **asthma**. The antibody levels in the serum of rats were measured by ELISA, and cell counts were done on cytospin preparations of bronchoalveolar lavage fluid. Body weight was decreased after allergen challenge in rats fed the amino acid mixture but not in rats fed the hypoallergenic flour. Antibody levels in the serum were significantly lower in rats fed hypoallergenic flour than in those fed the amino acid mixture. Differential cell counts in the bronchoalveolar lavage fluid showed that the numbers of eosinophils, lymphocytes, and neutrophils were significantly lower in rats fed the hypoallergenic flour than in those fed the amino acid mixture. These results suggest that hypoallergenic flour actively suppresses the allergic reactions; probably by inducing **oral tolerance**.

L38 ANSWER 17 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:305271 The Genuine Article (R) Number: 420GA. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Kalliomaki M (Reprint); Salminen S; Arvilommi H; Kero P; Koskinen P; Isolauri E. Turku Univ Hosp, Dept Paediat, POB 52, FI-20521 Turku, Finland (Reprint); Turku Univ Hosp, Dept Paediat, FI-20521 Turku, Finland; Univ Turku, Dept Paediat, Turku, Finland; Univ Turku, Dept Biochem & Food Chem, Turku, Finland; Univ Turku, Dept Clin Chem, Turku, Finland; Natl Publ Hlth Inst, Turku, Finland. LANCET (7 APR 2001) Vol. 357, No. 9262, pp. 1076-1079. Publisher: LANCET LTD. 84 THEOBALDS RD, LONDON WC1X 8RR, ENGLAND. ISSN: 0140-6736. Pub. country: Finland. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background Reversal of the progressive increase in frequency of atopic disease would be an important breakthrough for health care and wellbeing in western societies. In the hygiene hypothesis this increase is attributed to reduced microbial exposure in early life. Probiotics are cultures of potentially beneficial bacteria of the healthy gut microflora. We assessed the effect on atopic disease of Lactobacillus GG (which is safe at an early age and effective in treatment of allergic inflammation and food **allergy**).

Methods In a double-blind, randomised placebo-controlled trial we gave Lactobacillus GG prenatally to mothers who had at least one first-degree relative (or partner) with atopic eczema. allergic rhinitis, or **asthma**, and postnatally for 6 months to their infants. Chronic recurring atopic eczema, which is the main sign of atopic disease in the first years of life, was the primary endpoint.

Findings Atopic eczema was diagnosed in 46 of 132 (35%) children aged 2 years. **Asthma** was diagnosed in six of these children and allergic rhinitis in one. The frequency of atopic eczema in the probiotic group was half that of the placebo group (15/64 [23%] vs 31/68 [46%]; relative risk 0.51 [95% CI 0.32-0.84]). The number needed to treat was 4.5 (95% CI 2.6-15.6).

Interpretations Lactobacillus GG was effective in prevention of early atopic disease in children at high risk. Thus, gut microflora might be a hitherto unexplored source of natural immunomodulators and probiotics, for prevention of atopic disease.

L38 ANSWER 18 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:639003 The Genuine Article (R) Number: 460XY. Food **allergy** and atopic dermatitis in low birthweight infants during early childhood. Hikino S (Reprint); Nakayama H; Yamamoto J; Kinukawa N; Sakamoto M; Hara T . Kyushu Univ, Grad Sch Med Sci, Dept Pediat, Higashi Ku, 3-1-1 Maidashi, Fukuoka 8128582, Japan (Reprint); Kyushu Univ, Grad Sch Med Sci, Dept Pediat, Higashi Ku, Fukuoka 8128582, Japan; Kyushu Univ, Grad Sch Med Sci, Dept Med Informat, Fukuoka 8128582, Japan. ACTA PAEDIATRICA (AUG 2001) Vol. 90, No. 8, pp. 850-855. Publisher: TAYLOR & FRANCIS AS. CORT ADELERSGT 17, PO BOX 2562, SOLLI, 0202 OSLO, NORWAY. ISSN: 0803-5253. Pub. country: Japan. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The prevalence rates of food **allergy** and atopic dermatitis in low birthweight infants were evaluated. In Fukuoka City, Japan, between July 1994 and September 1997, sufficient information including birthweight, gestational age, sex, feeding method and a history of food **allergy** was obtained from questionnaires at the well-baby check-ups of 21766 infants (18 mo of age) and 4378 children (3 y of age). All the children were examined by pediatricians with regard to the existence of atopic dermatitis. The prevalence rate (8.1%) of rood **allergy** in infants with low birthweight (<2500 g) was significantly lower than that (11.2%) in infants with normal birthweight (<greater than or equal to>2500 g) at 18 mo of age (p = 0.0002). Atopic dermatitis was also observed at a lower prevalence rate (1.2%) in infants with low birthweight than in those with normal birthweight (2.3%) at the same age (p=0.0041). However, this significance was lost at 3 y of age. Other characteristics including male sex and breast-feeding showed independent risks for the development of food **allergy** and atopic dermatitis at both ages.
Conclusion: This study found that low birthweight wits significantly associated with a lower risk of both food **allergy** and atopic dermatitis at 18 mo of age.

L38 ANSWER 19 OF 28 MEDLINE on STN
2002228233. PubMed ID: 11964695. Sensitization and tolerance. Husby S. (Department of Pediatrics, Odense University Hospital, Denmark.. steffen.husby@ouh.fyns-amt.dk) . Current opinion in allergy and clinical immunology, (2001 Jun) 1 (3) 237-41. Journal code: 100936359. ISSN: 1528-4050. Pub. country: United States. Language: English.
AB The mechanisms responsible for sensitization, in particular within the gastrointestinal tract, are IgE-mediated as well as of a non-IgE-mediated, immunological origin. The phenomenon that is the opposite of sensitization is the maintenance of tolerance and is exemplified by the phenomenon **'oral tolerance'**. The cytokines transforming growth factor beta and interferon gamma have been shown to be key immunoregulatory cytokines in **oral tolerance**. A new experimental model of eosinophilic allergic gastroenteritis has been developed with the use of encapsulated dietary antigen. The model was used in mice with genetic deletions of the eosinophil chemokine eotaxin or of the cytokine IL-5, demonstrating the importance of eotaxin. In clinical **allergy** research, a major question has been to explain the global increase in **asthma** and **allergy**. The 'hygiene hypothesis' states that a lack of maturation of the infant immune system from a T helper 2 to a T helper 1 type of immune response may be caused by less microbial stimulation in Western societies. Several lines of data support this hypothesis. However, apart from the genetic constitution of the individual, breastfeeding in infancy may be the most important single determinant for the development of clinical tolerance.

L38 ANSWER 20 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:883863 The Genuine Article (R) Number: 488JV. Intranasal treatment with a recombinant hypoallergenic derivative of the major birch pollen allergen Bet v 1 prevents allergic sensitization and airway inflammation in mice. Wiedermann U (Reprint); Herz U; Baier K; Vrtala S; Neuhaus-Steinmetz U; Bohle B; Dekan G; Renz H; Ebner C; Valenta R; Kraft D. Univ Vienna, Dept Clin Pharmacol, AKH, Wahringer Guertel 18-20, A-1090 Vienna, Austria (Reprint); Univ Vienna, Dept Clin Pharmacol, AKH, A-1090 Vienna, Austria; Univ Vienna, Dept Pathophysiol, A-1090 Vienna, Austria; Univ Vienna, Dept Clin Pathol, A-1090 Vienna, Austria; Univ Marburg, Clinicum, Marburg, Germany. INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY (SEP 2001) Vol. 126, No. 1, pp. 68-77. Publisher: KARGER. ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND. ISSN: 1018-2438. Pub. country: Austria; Germany. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Background. The major birch pollen allergen Bet v 1 represents one of the most prevalent environmental allergens responsible for allergic airway inflammation. Objective: In the present study we sought to compare the complete recombinant Bet v 1 allergen molecule with genetically produced hypoallergenic fragments of Bet v 1 regarding mucosal tolerance induction in a mouse model of allergic **asthma**. Methods: BALB/c mice were intranasally treated with recombinant Bet v 1 or with two recombinant Bet v 1 fragments (F I: aa 1-74; F II: aa 75-160) prior to aerosol sensitization with birch pollen and Bet v 1. Results: Intranasal application of F II, containing the major T cell epitope, led to significant reduction of IgE/IgG1 antibody responses, in vitro cytokine production (IL-5, IFN-gamma, IL-10) and negative immediate cutaneous hypersensitivity reactions comparable to the pre-treatment with the complete rBet v 1 allergen. Moreover, airway inflammation (eosinophilia, IL-5) was inhibited by the pretreatment with either the complete Bet v 1 or F II. However, for prevention of airway hyperresponsiveness the complete molecule was required. The mechanisms leading to immunosuppression seemed to differ in their dependence on the conformation of the molecules, since tolerance induced with the complete Bet v 1, but not with F II, was transferable with spleen cells and associated with increased TGF-beta mRNA levels. Conclusion: We conclude that mucosal tolerance induction with recombinant allergens and genetically engineered hypoallergenic derivatives thereof could provide a convenient and safe intervention strategy against type I **allergy**. Copyright (C) 2001 S. Karger AG, Basel.

L38 ANSWER 21 OF 28 MEDLINE on STN
2001093223. PubMed ID: 11152571. Modulation of IgE response and cytokine production in Peyer's patches and draining lymph nodes in sensitized mice made tolerant by oral dust mite administration. Maciel M; Fusaro A E; Duarte A J; Sato M N. (Laboratorio de Alergia e Imunologia Clinica e Experimental/LIM-56, Faculdade de Medicina da Universidade de Sao Paulo-Brasil.) Journal of interferon & cytokine research : official journal of the International Society for Interferon and Cytokine Research, (2000 Dec) 20 (12) 1057-63. Journal code: 9507088. ISSN: 1079-9907. Pub. country: United States. Language: English.
AB Such allergic diseases as rhinitis and **asthma** are IgE-mediated type I reactions and are controlled primarily by Th2 cells. One of the major dust mites, Dermatophagoides pteronyssinus (Dp), is considered to cause allergic reactions. **Oral tolerance**, largely used to modulate immune response, opens the possibility of modulating Th2 allergic responses. We observed downmodulation of total and specific IgE antibody levels as well as the number of specific IgE-secreting cells with Dp feeding in previously sensitized mice. Analysis of the cytokine profile in mucosal lymphoid tissues in the protocol revealed altered patterns of interferon-gamma (IFN-gamma), interleukin-5 (IL-5), and transforming growth factor-beta (TGF-beta) secretion in Dp-fed animals.

The results suggest that both the Th and B cell populations are modulated in mice made tolerant by oral Dp feeding. Understanding the mechanisms at the mucosal level that underlie **oral tolerance** can improve its use in **allergy** immunotherapy.

L38 ANSWER 22 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:622438 The Genuine Article (R) Number: 343NH. Mechanisms preventing allergen-induced airways hyperreactivity: Role of tolerance and immune deviation. Tsitoura D C; Blumenthal R L; Berry G; DeKruyff R H; Umetsu D T (Reprint). STANFORD UNIV, MED CTR, DEPT PEDIAT, DIV CLIN IMMUNOL & ALLERGY, RM G309, STANFORD, CA 94305 (Reprint); STANFORD UNIV, MED CTR, DEPT PEDIAT, DIV CLIN IMMUNOL & ALLERGY, STANFORD, CA 94305; STANFORD UNIV, DIV IMMUNOL & TRANSPLANTAT BIOL, STANFORD, CA 94305; STANFORD UNIV, DEPT PATHOL, STANFORD, CA 94305. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (AUG 2000) Vol. 106, No. 2, pp. 239-246. Publisher: MOSBY, INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Aeroallergens continuously enter the respiratory tract of atopic individuals and provoke the development of **asthma** characterized by airway hyperreactivity; (AHR) and inflammation, By contrast, nonatopic individuals are exposed to the same aeroallergens, but airway inflammation does not develop, However, the mechanisms that prevent allergen-induced respiratory diseases in nonatopic subjects are poorly characterized.

Objective: In this study we compared the role of allergen-specific T-cell tolerance and immune deviation in conferring protection against the development of allergen-induced AHR,

Methods: We exposed mice to intranasal ovalbumin (OVA) to induce T-cell tolerance and examined its effects on the subsequent development of AHR and inflammation.

Results: We demonstrated that exposure of mice to intranasal OVA resulted in peripheral CD4(+) T-cell unresponsiveness that very efficiently prevented not only the development of AHR but also greatly inhibited airway inflammation and OVA-specific IgE production. The induction of peripheral T-cell tolerance and protection against AHR were not dependent on the presence of IFN-gamma or IL-4, The development of AHR was also prevented by an OVA-specific T(H)1-biased immune response induced by inhalation of OVA in the presence of IL-12, However, the OVA-specific T(H)1 response was associated with a significant degree of pulmonary inflammation.

Conclusion: These results indicate that both allergen-specific T-cell tolerance and T(H)1-biased immune deviation prevent the development of AHR, but T(H)1 responses are associated with significantly greater inflammation in the lung than is associated with T-cell unresponsiveness. Therefore CD4(+) T-cell unresponsiveness critically regulates immune responses to aeroallergens and protects against the development of allergic disease and **asthma**.

L38 ANSWER 23 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2000:569898 The Genuine Article (R) Number: 336UF. T-cell receptor V beta repertoire in mite-allergic subjects after sublingual immunotherapy. Mastrandrea F (Reprint); Coradduzza G; Serio G; Scarcia G; Minardi A. AOSS ANNUNZIATA, ALLERGY & CLIN IMMUNOL OPERAT UNIT, VIA BRUNO, I-74100 TARANTO, ITALY (Reprint). JOURNAL OF INVESTIGATIONAL ALLERGOLOGY & CLINICAL IMMUNOLOGY (MAY-JUN 2000) Vol. 10, No. 3, pp. 142-148. Publisher: PROUS SCIENCE, SA. PO BOX 540, PROVENZA 388, 08025 BARCELONA, SPAIN. ISSN: 1018-9068. Pub. country: ITALY. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Sublingual immunotherapy has been recognized as an alternative to injected immunotherapy for the treatment of allergic diseases. Even if compelling clinical evidence supports such a view, few studies are available on its mechanisms of action. This study was carried out to

investigate the peripheral lymphocyte V beta repertoire of subjects with mite-allergic respiratory **allergy** who were either not treated or treated for 2 years with mite-specific sublingual immunotherapy. The T-cell receptor V beta distribution was studied by flow-cytometric techniques in three subject groups. Group A (untreated) included 19 subjects with symptomatic, mile-allergic, low to moderate **asthma** and/or rhinitis. Group B (treated) was made up of 10 asymptomatic subjects treated for 2 years with mite-specific sublingual-swallow immunotherapy for low to moderate **asthma** and/or rhinitis. Group C (controls) included 10 healthy subjects. The V beta usage was investigated with monoclonal antibodies specific to the diverse beta segments V3, V5a, V5b, V5c, V6a, V8a, V8b and V12a. The comparison between the group A and group C repertoires showed a lower expression ($p < 0.05$) of the beta V8b+ T-cell subset The group B repertoire, when compared with group A, showed a significantly greater usage of the beta V5a ($p < 0.05$), 8a ($p < 0.05$) and 12a ($p < 0.01$) segments. The significantly lower expression of beta V8b observed in the symptomatic untreated group was not present in the group that was asymptomatic after treatment. The oligoclonal expansion observed in the treated group was consistent with the development of suppressor T-cell and/or of Th1 clones but not with deletion mechanisms of induced tolerance.

L38 ANSWER 24 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:213807 The Genuine Article (R) Number: 172VJ. New genetic and pathogenetic aspects of atopy. deWeck A L (Reprint); Derer M; Mayer P; Liehl E; Schiessl B; Zunic M; Schneider H. GERIMMUN FDN, 14 GRANDS PL, CH-1700 FRIBOURG, SWITZERLAND (Reprint); CMG HESKA ALLERGY PROD, FRIBOURG, SWITZERLAND. ALLERGOLOGIE (FEB 1999) Vol. 22, No. 2, pp. 92-97. Publisher: DUSTRI-VERLAG DR KARL FEISTLE. BAHNHOFSTRABE 9 POSTFACH 49, W-8024 MUNCHEN-DEISENHOFEN, GERMANY. ISSN: 0344-5062. Pub. country: SWITZERLAND. Language: German.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In studies of dog atopy, we have found that the high IgE responder status is inherited in a dominant manner. However, various environmental factors are required in addition to allow full expression of the gene. Such are a very early contact with some allergen to start the IgE response, allergen administration by injection and the absence of feeding with allergen during the first months of life. These observations show that the late determination of the allergic phenotype does not enable to make correct conclusions about the atopic genotype. Various factors which drive the dogs to IgE responses and atopy appear also to play a role in man.

L38 ANSWER 25 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1998:637035 The Genuine Article (R) Number: 110UB. Zug-Frauenfeld nutritional survey (''Zuff study''): Allergen-reduced nutrition in a normal infant population and its health-related effects: Results at the age of six months. Exl B M (Reprint); Deland U; Wall M; Preysch U; Secretin M C; Shmerling D H. NESTLE SUISSE SA, DEPT NUTR, CASE POSTALE 352, CH-1800 VEVEY, SWITZERLAND (Reprint); UNIV ZURICH, CHILDRENS HOSP, CH-8006 ZURICH, SWITZERLAND. NUTRITION RESEARCH (AUG 1998) Vol. 18, No. 8, pp. 1443-1462. Publisher: PERGAMON-ELSEVIER SCIENCE LTD. THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND. ISSN: 0271-5317. Pub. country: SWITZERLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Atopic diseases in childhood are on the increase. Much effort is thus being devoted to research into practical and feasible **allergy** -prevention programs. So far, the effects of adherence to an allergen-reduced diet for the first few months of life have mainly been studied in high-risk newborn populations. As the sensitivity and specificity of all feasible and practical screening parameters for selecting newborn populations with an elevated risk for **allergies** are still rather low, the possible inclusion of all newborns in prevention

programs, insofar as they are acceptable, or even of benefit for all, and cost-effective, is now a frequently discussed topic. Very little is known about the effects of adherence to such a diet in the first 4-6 months within a normal infant population.

We report on a prospective nutritional intervention study comparing neonates in an intervention group ((Z) under bar: breastfeeding (BF) and/or allergen-reduced (HA) infant formula, no weaning food, for 4 mths; n = 540) with a corresponding neonate control group (<(FF)under bar>: no specific feeding advice; n = 556) on the basis of certain growth criteria (weight, length, head circumference) and health criteria (overall, gastro, respiratory, skin). Allocation to groups was based on exclusive breastfeeding (BF) (Z = 227, FF = 162). partial-BF (Z = 196; FF = 311) or non-BF (Z = 43, FF = 62). Important adjuvant and structural factors were compared for both populations. Nutritional surveillance took place via regular entries in diet journals over the entire first 12 months. Growth- and health-related data were entered by specially trained pediatricians and evaluated by a special computer program. Statistical group comparisons were based on odds ratios and CI's and additional factors of influence were taken into account as covariates via logistic regression.

Growth was almost identical in the Z and FF groups. At 6 months, the total number of infants with health-related entries was lower in Z than in FF (33 vs 50 %; $p < 0.0001$; OR = 0.6; 95% CI: 0.6 - 0.8. worst- case analysis), the main difference being the ''skin'' results (12 vs 28%). During the intervention period, no difference was seen in the BF groups (29 vs 31%; control for reliability with confounders, OR = 1.1; 95% CI: 0.7 - 1.7). The partial-BF and non-BF groups in Zug were at an advantage over those in FF after 6 months (34 vs 46%, OR = 0.6, 95% CI: 0.4 - 0.8, and 28 vs 57%, OR = 0.3, 95% CI: 0.1 - 0.7), mainly due to the ''skin'' results. In summary, we showed that general health status, even in a normal infant population, is enhanced by an allergen-reduced diet, the main difference being fewer skin problems; a dietary regime of this type should thus be encouraged in future for all non- or partially breastfed infants. (C) 1998 Elsevier Science Inc.

L38 ANSWER 26 OF 28 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
1998:212454 Document No.: PREV199800212454. Prevention of lung eosinophilic inflammation by **oral tolerance**. Russo, Momtchilo [Reprint author]; Jancar, Sonia; Siqueira, Ana Lucia Pereira De; Mengel, Jose; Gomes, Eliane; Ficker, Sabine Madsen; Faria, Ana Maria Caetano De. Dep. Imunol., Inst. Cienc. Biomedicas, ICB-III, Univ. de Sao Paulo, Av. Professor Lineu Prestes 2415, 05508-900 Sao Paulo, SP, Brazil. Immunology Letters, (March, 1998) Vol. 61, No. 1, pp. 15-23. print.
CODEN: IMLED6. ISSN: 0165-2478. Language: English.

AB Airway inflammation plays a major role in human **asthma**. Increasing evidence points to a close correlation between eosinophil infiltration and allergic lung disease. A new murine model of eosinophilic lung inflammation has recently been developed; it consists of immunizing mice with small fragments of solidified hen egg white implanted (EWI) into the subcutaneous tissue. In this model, which is further characterized here, mice challenged with ovalbumin (OVA) present an intense and persistent lung eosinophilia, as well as histopathological findings that resemble human **asthma**. In the present work, the effect of **oral tolerance** on the development of allergic lung inflammation in B6 mice immunized with antigen plus adjuvant or with EWI is investigated. It was found that in mice rendered orally tolerant by previous exposure to antigen in the drinking water, the T-helper type 2 cell (Th2)-associated allergic responses in both protocols of immunization were almost completely abolished. The allergic responses were assessed by pulmonary and bone marrow eosinophilia, lung histopathology and antigen-specific IgE and IgG1 production. These findings provide the first indication that Th2-associated lung pathology can be prevented by **oral tolerance**.

L38 ANSWER 27 OF 28 MEDLINE on STN
1998026170. PubMed ID: 9379048. TGF-beta induced by **oral tolerance** ameliorates experimental tracheal eosinophilia. Haneda K; Sano K; Tamura G; Sato T; Habu S; Shirato K. (First Department of Internal Medicine, Tohoku University School of Medicine, Sendai, Japan.) Journal of immunology (Baltimore, Md. : 1950), (1997 Nov 1) 159 (9) 4484-90. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Induction of peripheral tolerance is one of the feasible approaches for the control of autoimmunities and **allergies**. Therapeutic applications of **oral tolerance** to autoimmunities are in progress both experimentally and clinically, while those to **allergies** have been poorly investigated. We examined the induction of CD4+ T cells with suppressive properties by **oral tolerance** and the mechanism by which these cells down-regulated Ag-induced eosinophilia in the trachea. Feeding of mice transgenic for anti-OVA TCR with high doses of OVA inhibited the airway eosinophilic inflammation induced by the intratracheally administered Ag. This inhibition reflected the mechanism of active suppression, since the inhibitory effect was adoptively transferred by splenic CD4+ T cells from the transgenic mice fed with high doses of OVA. The Ag specificity of the suppressor T cells was documented by the failure of spleen cells from mice that were orally tolerant of OVA to suppress irrelevant Ag, KLH-specific airway eosinophilic inflammation. The suppressive effect of the transferred T cells on eosinophil recruitment was neutralized by anti-TGF-beta mAb, but not anti-IFN-gamma mAb, indicating that the suppression is due to the inhibitory effect by secreted TGF-beta, but not to the dominance of the transferred Th1 cells over Th2 cells. This is the first study to reveal a link between **oral tolerance** and the regulation of Th2-mediated experimental tracheal eosinophilia through TGF-beta. Our experimental model suggests possible therapeutic applications of **oral tolerance** for the treatment of allergic disorders such as bronchial **asthma**.

L38 ANSWER 28 OF 28 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
96:316245 The Genuine Article (R) Number: UF493. IMMUNE FUNCTIONS AND IMMUNOPATHOLOGY OF THE MUCOSA OF THE UPPER RESPIRATORY PATHWAYS. BRANDTZAEG P (Reprint); JAHNSEN F L; FARSTAD I N. UNIV OSLO, INST PATHOL, NATL HOSP, RIKSHOSP, LAB IMMUNOHISTOCHEM & IMMUNOPATHOL, N-0027 OSLO, NORWAY (Reprint). ACTA OTO-LARYNGOLOGICA (MAR 1996) Vol. 116, No. 2, pp. 149-159. ISSN: 0001-6489. Pub. country: NORWAY. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The specific defence of airway mucosae depends primarily on secretory immunity. The B cells involved are initially stimulated in organized mucosa-associated lymphoid tissue, apparently including the tonsils and adenoid. From these inductive sites, memory cells migrate to secretory effector sites where they differentiate terminally to immunoglobulin (Ig)-producing plasma cells. Locally produced Ig consists mainly of J chain-containing dimers and larger polymers of IgA (pIgA) that are selectively transported through glandular cells by an epithelial receptor called secretory component or the pig receptor. IgG can participate in immune exclusion because it reaches the secretions by passive diffusion. However, its proinflammatory properties render IgG antibodies of local immunopathological importance when elimination of penetrating antigens is unsuccessful. T helper (Th) cells activated in this process may by a Th2 cytokine profile promote persistent inflammation with extravasation and priming of eosinophils. This development appears to be part of the late-phase allergic reaction, perhaps initially driven by interleukin-4 (IL-4) released from mast cells that are subjected to IgE-mediated activation, and subsequently also by Th2 cell activation. Eosinophils are potentially tissue-damaging, particularly after priming with IL-5. Various cytokines up-regulate adhesion molecules on endothelial and epithelial cells, thereby enhancing migration of eosinophils into the mucosa, and

perhaps in addition causing aberrant immune regulation within the epithelium. Soluble antigens bombarding the epithelial surfaces normally seem to induce several immunosuppressive mechanisms, but mucosal homeostasis appears less patent in the airways than **oral tolerance** to dietary antigens operating in the gut.

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L40 ANSWER 1 OF 16 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2003:300973 The Genuine Article (R) Number: 661NU. Breast milk fatty acids, eicosanoids, and cytokines in mothers with and without allergic disease. Laiho K (Reprint); Lampi A M; Hamalainen M; Moilanen E; Piironen V; Arvola T; Syrjanen S; Isolauri E. Univ Turku, Dept Pediat, POB 52, Turku 20521, Finland (Reprint); Univ Turku, Dept Paediat, Turku 20521, Finland; Univ Turku, Inst Dent, Turku 20521, Finland; Univ Helsinki, Dept Appl Chem & Microbiol, Helsinki, Finland; Univ Tampere, Immunopharmacol Res Grp, Sch Med, FIN-33101 Tampere, Finland; Univ Tampere, Dept Pediat, FIN-33101 Tampere, Finland; Tampere Univ Hosp, Tampere, Finland. PEDIATRIC RESEARCH (APR 2003) Vol. 53, No. 4, pp. 642-647. Publisher: INT PEDIATRIC RESEARCH FOUNDATION, INC. 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436 USA. ISSN: 0031-3998. Pub. country: Finland. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Allergic disease (AD), including atopic **eczema**, asthma, allergic rhinitis, and food **allergy**, is characterized by an imbalance between cytokines produced by distinct T-helper cell subtypes. Whether this imbalance can be transferred from mother to breast milk remains to be established. The objective was to investigate the concentrations and interactions of nutritional and inflammatory factors in breast milk. Breast milk samples were collected from mothers with AD (n = 43) and without AD (n = 51). The concentrations of transforming growth factor (TGF)-beta(2), tumor necrosis factor-alpha, IL-4, IL-10, prostaglandin E-2 and cysteinyl leukotrienes were measured by immunoassays and fatty acid composition by gas chromatography. Mothers with AD had a lower concentration of TGF-beta(2) in breast milk [median (interquartile range), 420 (278-701) ng/L] compared with those without AD [539 (378-1108) ng/L; p = 0.003], whereas other cytokines, prostaglandin E-2, and cysteinyl leukotriene concentrations or fatty acid composition were not significantly different between the groups. The breast milk inflammatory factors and fatty acid composition were shown to be related. A positive association was observed between TGF-beta(2) and the proportion of polyunsaturated fatty acids (p = 0.038) and a negative association between TGF-beta(2) and the proportion of saturated fatty acids (p = 0.029) in breast milk. The reduced TGF-beta(2) concentration in the breast milk of mothers with AD may interfere with the development of the mucosal immune system of the breast-fed infant. The observed associations between nutritional and inflammatory factors in breast milk suggest that it may be possible to influence the immunologic properties of breast milk by dietary intervention of the mother.

L40 ANSWER 2 OF 16 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2004034215 EMBASE **Oral Tolerance**. Wu H.Y.; Weiner H.L..
H.L. Weiner, Center for Neurologic Disease, Brigham and Women's Hospital, HIM730, 77 Avenue Louis Pasteur, Boston, MA 02115, United States. hweiner@rics.bwh.harvard.edu. Immunologic Research 28/3 (265-284) 2003.

Refs: 143.
ISSN: 0257-277X. CODEN: IMRSEB. Pub. Country: United States. Language: English. Summary Language: English.

AB Autoimmune conditions caused by injurious immune responses against self-antigens can be ameliorated if the inappropriate responses to self-components that cause tissue injury can be modulated by regulatory cells or shut off via the induction of anergy or via deletion of pathogenic immune responses. Antigen encounter at the gut mucosa can lead to suppression of injurious immune responses to self-antigen via these mechanisms. This type of immunological event is termed **oral tolerance**. In this review, we examine the mechanisms behind the induction of **oral tolerance** and provide findings from its use as a form of treatment for autoimmune diseases.

L40 ANSWER 3 OF 16 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2002:713060 The Genuine Article (R) Number: 584VP. Probiotics and **allergy**. Hauer A C (Reprint). Graz Univ, Klin Kinder & Jugendheilkunde, Dept Allgemeine Padiatrie, Auenbruggerpl, A-8036 Graz, Austria (Reprint); Graz Univ, Klin Kinder & Jugendheilkunde, Dept Allgemeine Padiatrie, A-8036 Graz, Austria. MONATSSCHRIFT KINDERHEILKUNDE (JUL 2002) Vol. 150, No. 7, pp. 829-+. Publisher: SPRINGER-VERLAG. 175 FIFTH AVE, NEW YORK, NY 10010 USA. ISSN: 0026-9298. Pub. country: Austria. Language: German.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB For years there has been an increasing interest in the potential use of probiotics in **allergy** prevention and treatment, as they seem to influence the pathomechanisms leading to allergic disease at various levels: Probiotics stimulate the physiological intestinal flora necessary for maturation of the intestinal immune system and they help stabilise the intestinal barrier. They also induce specific and unspecific defense mechanisms in the gut, i.e. antigen specific humoral immune responses, and seem to counteract the dominance of the atopy-associated Th2-type cytokine profile. Therefore they could be of particular importance for newborns and infants in our part of the world, whose intestinal flora - due to environmental factors - has changed in composition and maturation, thus affecting the development of intestinal immune functions. Some smaller controlled studies have shown a clear clinical benefit of probiotics for infants with atopic dermatitis - both in terms of prevention and treatment. However, further experimental work is needed to explain the exact underlying mechanisms and clinical studies should demonstrate the various clinical effects of probiotics on a broader level, before they can be generally recommended in the context of **allergy**.

L40 ANSWER 4 OF 16 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2002:896135 The Genuine Article (R) Number: 607PL. Leucocytes in human milk and lymphocyte subsets in cow's milk-allergic infants. Jarvinen K M (Reprint); Suomalainen H. CUNY Mt Sinai Sch Med, Div Pediat Allergy & Immunol, Box 1198, 1 Gustave L Levy Pl, New York, NY 10029 USA (Reprint); Univ Helsinki, Cent Hosp, Skin & Allergy Hosp, Dept Dermatol, Helsinki, Finland. PEDIATRIC ALLERGY AND IMMUNOLOGY (AUG 2002) Vol. 13, No. 4, pp. 243-254. Publisher: BLACKWELL MUNKSGAARD. 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK. ISSN: 0905-6157. Pub. country: USA; Finland. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The breast-fed infant ingests an average of 10(8) leucocytes per day, with breast-feeding often continuing for several months. The precise role of human milk leucocytes is still unresolved. Breast-feeding has been recommended for infants at high risk of **allergy** to prevent or delay the development of food **allergies** and atopic **eczema**. However, studies dealing with distinct immunologic factors in the mother's milk, and their effect on health status or development of **allergies** in the infant, are scarce. We evaluated the relationship between the cellular composition of human milk and development of cow's

milk **allergy** (CMA) in the breast-fed infant. Leucocyte subsets in the breast-fed infants were also measured. The study population comprised 61 breast-feeding mothers and their infants. Thirty-nine mothers each had a cow's milk-allergic infant, 10 had an infant with atopic dermatitis without CMA, and 12 mothers had a healthy infant. Leucocyte subsets in mothers' milk were counted using a light microscope and confirmed by flow cytometry. In infants, peripheral blood lymphocyte subsets were determined by flow cytometry and were correlated with the health status of the breast-fed infant and leucocyte composition of the mother's milk. Human milk was found to be a non-homogenous morphological entity. In the milk of mothers of infants with CMA, the proportion of macrophages was significantly smaller than in the mothers with infants without CMA(p = 0.036, t-test). Mothers with high proportions of neutrophils in their milk (>20%) had significantly more often infants with CMA than did those with low proportions of neutrophils (p = 0.02; Fischer's exact test). Eosinophils comprising. >1% of milk cells were only detected in the mothers who had infants with CMA. Furthermore, the proportions of CD4(+) T cells were positively correlated with the proportion of milk macrophages and negatively with the percentage of milk neutrophils and eosinophils. The proportions of total B cells and those expressing CD23, a low-affinity immunoglobulin E receptor, were positively correlated with the proportions of neutrophils and eosinophils in mother's milk and negatively with the percentage of milk macrophages. To conclude, the composition of breast milk in some mothers is abnormal and correlates with a diagnosis of CMA in a breast-fed infant. This may provide a new and interesting insight into the development of food **allergies**.

L40 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
2002:416993 Document No. 137:351635 Cow's milk (Bos domesticus). Besler, Matthias; Eigenmann, Philippe; Schwartz, Robert H. (Hamburg, Germany). Internet Symposium on Food Allergens [online computer file], 4(1), 19-106 (English) 2002. CODEN: ISFAF8. ISSN: 1437-0573. URL: http://www.food-allergens.de/symposium-4-1/cows-milk/cows-milk-allergens.htm Publisher: Internet Symposium on Food Allergens.

AB A review. Cow's milk **allergy** (CMA) can be defined as any adverse reaction mediated by immunol. mechanisms to cow's milk proteins. CMA can be divided in IgE-mediated reactions (IgE-CMA) and non-IgE-mediated reactions (non-IgE-CMA) which may involve other Igs, immune complexes and cell-mediated reactions. Patients with non-IgE-CMA and digestive symptoms can present with the following well defined clin. pictures: milk-induced enterocolitis, milk-induced proctitis, milk-induced enteropathy, or eosinophilic allergic gastro-enteritis. CMA should be differentiated from cow' milk intolerance (CMI) reactions due to lactase deficiency or other non immune mediated causes which are not subject of the present review. Most CMA has its onset in the first year of life, and becomes apparent at the time of weaning from breastfeeding. Prevalences of DMA range from 1.6% to 2.8% in randomly selected children younger than 2 yr of age (elimination/challenge proven). **Oral tolerance** is frequently acquired in about 50 to 90% of children with CMA within the first 6 yr of life. However, severe CMA may persist into adulthood. The frequency of sensitization to cow's milk in adults has recently been estimated by RAST to be 0.7% and 1.2% in Scandinavian countries. According to the onset of symptoms after milk ingestion CMA can be classified as immediate or delayed-type. The clin. picture can vary from mild to severe, involving the skin (**eczema**, hives, angioedema), gastrointestinal tract (oral pruritis, colic, vomiting, diarrhea, constipation), respiratory tract (cough, stridor, wheezing), and cardiovascular system (anaphylactic shock). No single laboratory test is diagnostic of CMA. Clin. manifestations supported by skin tests and in vitro parameters are valuable. The diagnosis is confirmed by well-defined elimination and subsequent challenge procedures. If there is evidence of anaphylaxis, challenge should be avoided. The inadvertent ingestion of small amts. of cow's milk allergens hidden in foods can result in severe

life-threatening clin. reactions. Cow's milk allergens could be present in breast milk, infant formulas, milk and milk products like cheese and yogurt, as well as in "non-dairy" foods occurring as contaminants or unlabeled additives. The most effective treatment of CMA is allergen avoidance. Besides the optimal choice of breast milk, suitable milk substitutes in the nutrition of infants with CMA are soy hydrolyzed formulas, extensively casein and whey hydrolyzed formulas, and amino acid formulas. The exact frequency of sensitization to soy protein in children with CMA is still controversial. Soy **allergy** seems to be rare in IgE-CMA, while approx. 60% of children with milk-induced enterocolitis are sensitive to soybean. However, severe anaphylactic reactions to extensively hydrolyzed casein and partially hydrolyzed whey formulas can occur in highly sensitized infants with IgE-mediated cow's milk **allergy**. Due to the high homol. of protein composition sheep's and goat's milk are cross-reactive in approx. 80% of subjects with CMA while mare's milk is only rarely cross-reactive with cow's milk (4% in subjects with CMA). In addition, sheep's milk may cause severe IgE-mediated allergic reactions in children not affected by CMA. IgE antibodies from children allergic to cow's milk are capable of recognizing milk proteins from mammals bred in European countries (ewe, goat, buffalo). Cross-reactivity of camel's milk proteins has not bee recognized. Therefore, due to clin. important residual allergenicity in some hypoallergenic formulas and milk allergen cross-reactivity between species, clin. testing in a safe medically-supervised environment is necessary in each cow's milk sensitive infant before use. In infants and children the major cow's milk allergens are casein (CAS), β-lactoglobulin (beta-LG), and α-lactalbumin (alpha-LA). Caseins (α-, β-, κ-CAS) are the most important in children and adults. Other allergens involved in SMA are bovine serum albumin (BSA) and bovine Igs. Several IgE-binding epitopes of α-LA, β-LG, α- and β-CAS were described.
Knowledge of the immunodominant epitopes of the major allergens may be useful in identifying children who will have persistent CMA and children who aer likely to outgrow CMA. The present data collection summarizes the following topics of the major allergens may be useful in identifying children who will have persistent CMA and children who are likely to outgrow CMA. The present data collection summarizes the following topics in tabular form: prevalences of DMA, diagnostic and therapeutic features, mol. biol. and allergenic properties of cow's milk allergens, stability and hidden presence of allergens, the use of infant formulas in therapy and prevention of CMA and other atopic diseases.

L40 ANSWER 6 OF 16 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:305271 The Genuine Article (R) Number: 420GA. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Kalliomaki M (Reprint); Salminen S; Arvilommi H; Kero P; Koskinen P; Isolauri E. Turku Univ Hosp, Dept Paediat, POB 52, FI-20521 Turku, Finland (Reprint); Turku Univ Hosp, Dept Paediat, FI-20521 Turku, Finland; Univ Turku, Dept Paediat, Turku, Finland; Univ Turku, Dept Biochem & Food Chem, Turku, Finland; Univ Turku, Dept Clin Chem, Turku, Finland; Natl Publ Hlth Inst, Turku, Finland. LANCET (7 APR 2001) Vol. 357, No. 9262, pp. 1076-1079. Publisher: LANCET LTD. 84 THEOBALDS RD, LONDON WC1X 8RR, ENGLAND. ISSN: 0140-6736. Pub. country: Finland. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background Reversal of the progressive increase in frequency of atopic disease would be an important breakthrough for health care and wellbeing in western societies. In the hygiene hypothesis this increase is attributed to reduced microbial exposure in early life. Probiotics are cultures of potentially beneficial bacteria of the healthy gut microflora. We assessed the effect on atopic disease of Lactobacillus GG (which is safe at an early age and effective in treatment of allergic inflammation and food **allergy**).

Methods In a double-blind, randomised placebo-controlled trial we gave Lactobacillus GG prenatally to mothers who had at least one first-degree

relative (or partner) with atopic **eczema**. allergic rhinitis, or asthma, and postnatally for 6 months to their infants. Chronic recurring atopic **eczema**, which is the main sign of atopic disease in the first years of life, was the primary endpoint.

Findings Atopic **eczema** was diagnosed in 46 of 132 (35%) children aged 2 years. Asthma was diagnosed in six of these children and allergic rhinitis in one. The frequency of atopic **eczema** in the probiotic group was half that of the placebo group (15/64 [23%] vs 31/68 [46%]; relative risk 0.51 [95% CI 0.32-0.84]). The number needed to treat was 4.5 (95% CI 2.6-15.6).

Interpretations Lactobacillus GG was effective in prevention of early atopic disease in children at high risk. Thus, gut microflora might be a hitherto unexplored source of natural immunomodulators and probiotics, for prevention of atopic disease.

L40 ANSWER 7 OF 16 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
2001:639003 The Genuine Article (R) Number: 460XY. Food **allergy** and atopic dermatitis in low birthweight infants during early childhood. Hikino S (Reprint); Nakayama H; Yamamoto J; Kinukawa N; Sakamoto M; Hara T . Kyushu Univ, Grad Sch Med Sci, Dept Pediat, Higashi Ku, 3-1-1 Maidashi, Fukuoka 8128582, Japan (Reprint); Kyushu Univ, Grad Sch Med Sci, Dept Pediat, Higashi Ku, Fukuoka 8128582, Japan; Kyushu Univ, Grad Sch Med Sci, Dept Med Informat, Fukuoka 8128582, Japan. ACTA PAEDIATRICA (AUG 2001) Vol. 90, No. 8, pp. 850-855. Publisher: TAYLOR & FRANCIS AS. CORT ADELERSGT 17, PO BOX 2562, SOLLI, 0202 OSLO, NORWAY. ISSN: 0803-5253. Pub. country: Japan. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB The prevalence rates of food **allergy** and atopic dermatitis in low birthweight infants were evaluated. In Fukuoka City, Japan, between July 1994 and September 1997, sufficient information including birthweight, gestational age, sex, feeding method and a history of food **allergy** was obtained from questionnaires at the well-baby check-ups of 21766 infants (18 mo of age) and 4378 children (3 y of age). All the children were examined by pediatricians with regard to the existence of atopic dermatitis. The prevalence rate (8.1%) of rood **allergy** in infants with low birthweight (<2500 g) was significantly lower than that (11.2%) in infants with normal birthweight (<greater than or equal to>2500 g) at 18 mo of age (p = 0.0002). Atopic dermatitis was also observed at a lower prevalence rate (1.2%) in infants with low birthweight than in those with normal birthweight (2.3%) at the same age (p=0.0041). However, this significance was lost at 3 y of age. Other characteristics including male sex and breast-feeding showed independent risks for the development of food **allergy** and atopic dermatitis at both ages.

Conclusion: This study found that low birthweight wits significantly associated with a lower risk of both food **allergy** and atopic dermatitis at 18 mo of age.

L40 ANSWER 8 OF 16 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2001:506932 Document No.: PREV200100506932. **Oral tolerance** induction by low-dose nickel solution. Effective and safe treatment of nickel-induced **eczema**. Speciani, A. F. [Reprint author]; Fasani, G. [Reprint author]; Fumagalli, M. [Reprint author]; Barbieri, G. [Reprint author]; Gessati, A. [Reprint author]. Assoc. Medical Services, SMA, Milano, Italy. Allergy (Copenhagen), (2001) Vol. 56, No. Supplement 68, pp. 146. print.
Meeting Info.: XXth Congress of the European Academy of Allergology and Clinical Immunology. Berlin, Germany. May 09-13, 2001.
CODEN: LLRGDY. ISSN: 0105-4538. Language: English.

L40 ANSWER 9 OF 16 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2001201656 EMBASE The immunologic basis for intestinal food **allergy**

. Murch S.H.. Dr. S.H. Murch, Royal Free/Univ. Coll. Sch. of Med., Royal Free Campus, Rowland Hill Street, London NW3 2PF, United Kingdom. s.murch@rfc.ucl.ac.uk. Current Opinion in Gastroenterology 16/6 (552-557) 2000.
Refs: 74.
ISSN: 0267-1379. CODEN: COGAEK. Pub. Country: United States. Language: English. Summary Language: English.

AB There has been considerable recent broadening of basic concepts of intestinal food **allergy**, in particular the importance of non-IgE-mediated mechanisms. The traditional emphasis or IgE-mediated **allergy** now appears inappropriate in light of current studies of the basic mechanisms of **oral tolerance** to dietary antigen and of increasing recognition of the requirement for early infectious challenge in the prevention of allergic sensitization. This major change in emphasis has been forced both by basic scientific studies and by recognition of novel patterns of food allergic disease within the pediatric population, in which rapid increase in food-allergic sensitization has been noted in the last decade and previously rare phenomena such as multiple food **allergies** and sensitization of exclusively breast-fed infants to antigens eaten by the mother have become commonplace. It is thus emerging that the possession of exaggerated IgE responses may not be the direct cause of food allergic sensitization but may ensure that such sensitization is clinically obvious. Those without such immediate responses have a complex of symptoms, including diet-responsive **eczema** and a marked disturbance of intestinal motility. The clear demographic links with socioeconomic privilege and relative protection from gastrointestinal infactions concord with recent murine data suggesting an obligatory input from innate immune responses to the gut flora in the establishment of **oral tolerance**.

L40 ANSWER 10 OF 16 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2000:230416 Document No.: PREV200000230416. **Oral tolerance** of nickel in patients with dyshidrosis. Prystupa, K. [Reprint author]; Rudzki, E. [Reprint author]. Department of Dermatology, Warsaw School of Medicine, Koszykowa 82a, Warsaw, Poland. Contact Dermatitis, (May, 2000) Vol. 42, No. 5, pp. 276-277. print.
CODEN: CODEDG. ISSN: 0105-1873. Language: English.

L40 ANSWER 11 OF 16 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
1999:696979 The Genuine Article (R) Number: 233QX. Per os desensitization for nickel contact hypersensitivity double-blind placebo-controlled clinico-biological study. Bagot M (Reprint); Terki N; Bacha S; Moyse D; Suck C; Revuz J. HOP HENRI MONDOR, SERV DERMATOL, 51 AVE MARECHAL DE LATTRE DE TASSIGNY, F-94010 CRETEIL, FRANCE (Reprint); LAB LABCATAL, MONTROUGE, FRANCE. ANNALES DE DERMATOLOGIE ET DE VENEREOLOGIE (JUN-JUL 1999) Vol. 126, No. 6-7, pp. 502-504. Publisher: MASSON EDITEUR. 120 BLVD SAINT-GERMAIN, 75280 PARIS 06, FRANCE. ISSN: 0151-9638. Pub. country: FRANCE. Language: French.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background. Ingestion of nickel (Ni) has been demonstrated to induce a specific state of tolerance in the guinea pig and mouse; In a pilot study conducted in to patients, we demonstrated that per os administration of Ni leads to reduced proliferation of specific lymphocytes and a lower number of responding lymphocytes in blood. The aim of this study was to evaluate the clinical and biological changes induced by the ingestion of Ni in a double-blinded placebo-controlled study.

Patients and methods. patients with nickel contact hypersensitivity were given a capsule of nickel sulfate containing 5 mg Ni (group A) or an identical placebo (group B) once a week for 7 weeks. Clinical criteria were assessed 49 days after study onset: objective measurement of lesion extent and intensity and quantitative patch tests at concentrations 2.4-0.8-0.2 and 0.05 p. 100. Likewise stimulation of specific lymphocyte

proliferation and the number of circulating lymphocytes responding to Ni at limit dilutions were determined.

Results. Thirty patients with nickel contact **eczema** were included in the study, 28 women and 2 men. There was no statistical difference between the two groups for the intensity of skin lesions or their clinical course, quantitative patch tests and lymphocyte stimulation tests. Conversely, the number of circulating lymphocytes responding to Ni was significantly lower in group A than in group B at study end ($p < 0.05$).

Discussion. This double-blind placebo-controlled study confirmed that par os nickel can induce a significant reduction in the number of circulating lymphocytes responding to Ni. No other effect could be demonstrated for the clinical and biological parameters studied. These preliminary results should prompt a multicentric controlled trial including a larger number of patients with more severe lesions at inclusion and with a longer treatment duration.

L40 ANSWER 12 OF 16 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

2000:713738 The Genuine Article (R) Number: 354GL. Probiotics: towards demonstrating efficacy. MattilaSandholm T (Reprint); Blum S; Collins J K; Crittenden R; deVos W; Dunne C; Fonden R; Grenov G; Isolauri E; Kiely B; Marteau P; Morelli L; Ouwehand A; Reniero R; Saarela M; Salminen S; Saxelin M; Schiffrin E; Shanahan F; Vaughan E; vonWright A. VTT BIOTECHNOL, POB 1500, FIN-02044 ESPOO, FINLAND (Reprint); NESTEC LTD, NESTLE RES CTR, CH-1000 LAUSANNE 26, SWITZERLAND; UNIV COLL CORK, DEPT MICROBIOL, CORK, IRELAND; UNIV COLL CORK, DEPT MED, CORK, IRELAND; NATL FOOD BIOTECHNOL CTR, CORK, IRELAND; UNIV WAGENINGEN & RES CTR, MICROBIOL LAB, NL-6703 CT WAGENINGEN, NETHERLANDS; ARLA R&D, S-10546 STOCKHOLM, SWEDEN; CHR HANSEN AS, DK-2970 HORSHOLM, DENMARK. TRENDS IN FOOD SCIENCE & TECHNOLOGY (DEC 1999) Vol. 10, No. 12, pp. 393-399. Publisher: ELSEVIER SCIENCE LONDON. 84 THEOBALDS RD, LONDON WC1X 8RR, ENGLAND. ISSN: 0924-2244 . Pub. country: FINLAND; SWITZERLAND; IRELAND; NETHERLANDS; SWEDEN; DENMARK. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB PROBDEMO, a multi-centre European research project, began in 1996 with the aim of demonstrating that probiotic microorganisms can positively effect human health in rigorously conducted human clinical studies. These studies, now completed, have shown that some probiotics can influence the composition of the intestinal microbiota and modulate the host immune system with measurable benefits to health, including the control of atopic **eczema** in infants with food **allergy**. Considerable promise was also demonstrated for the use of selected probiotics in controlling inflammatory bowel disease, and infections in children and the elderly. The scientific approaches to selecting and evaluating probiotics that were demonstrated in the PROBDEMO project provide a model for food manufacturers to move further towards demonstrating efficacy for their probiotic products.

L40 ANSWER 13 OF 16 EMBASE on STN

97353430 EMBASE Document No.: 1997353430. [Food **allergy**, intolerance and prevention of atopic diseases]. NAHRUNGSMITTELALLERGIE, INTOLERANZ UND PRAVENTION ATOPISCHER KRANKHEITEN. Strobel S.. Prof. Dr. S. Strobel, Immunobiology Unit, Institute of Child Health, London WC1N 1EH, United Kingdom. Allergologie 20/11 (565-570) 1997.
Refs: 39.
ISSN: 0344-5062. CODEN: ALLRDI. Pub. Country: Germany. Language: German. Summary Language: German; English.

AB About 2% of children in Europe suffer from cow's milk **allergy**, and 5% of the adult population suffer from food-induced clinical symptoms. Food **allergy** is often a disease of infancy and childhood. It can be simplified as a breakdown of **oral tolerance** or failure of its introduction. Mucosal antigen exposure generally leads to 3

important immunoregulatory processes which are not entirely understood. These are immune exclusion, immune elimination, and immune regulation (**oral tolerance**), which can be defined as antigen-specific hypo- or non-reactivity after prior mucosal (intestinal) exposure. The induction of **oral tolerance** is an active process which is finely tuned by the intestinal epithelium (including intraepithelial lymphocytes), specialized antigen-presenting cells, and lymphocytes of the lamina propria. Different immunological processes are induced depending on the nature of the antigen, frequency and dose of administration, and the age of the individual. Administration of 'low' antigen doses is associated with induction of suppressor cells which secrete regulatory cytokines such as TGF-β and IL-4, IL-5, and others (Th2 type). However, antigen administration also leads so suppression of IgG, IgE, and cell-mediated immune responses, which suggest a suppression of Th1- and Th2-dependent mechanisms. Anergy, clonal deletion, and other forms of immune deviation can be a part of the suppression of systemic immunity after mucosal antigen exposure. IgE and cell-mediated immune responses are implicated in a majority of clinical symptoms. The skin, the gastrointestinal tract, and the lungs are most commonly affected with clinical features ranging from mild to severe generalized (at times fatal) anaphylactic reactions. The incidence of milk **allergy**- and other food-induced symptoms in infancy have led to the design of nutritional prophylactic strategies with heat-denatured and enzyme-digested milk formulae on whey and casein basis with different degrees of hydrolysis. A number of prospective, randomized, and placebo-controlled clinical feeding studies seem to indicate a reduction in the incidence of milk **allergies** and of atopic **eczema** in infants of families with a positive atopic history (parent and/or sibling).

L40 ANSWER 14 OF 16 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
97:161958 The Genuine Article (R) Number: WH831. Probiotics: A novel approach in the management of food **allergy**. Majamaa H; Isolauri E (Reprint). TAMPERE UNIV, SCH MED, POB 607, FIN-33101 TAMPERE, FINLAND (Reprint); TAMPERE UNIV, SCH MED, FIN-33101 TAMPERE, FINLAND; TAMPERE UNIV HOSP, DEPT PEDIAT, TAMPERE, FINLAND. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (FEB 1997) Vol. 99, No. 2, pp. 179-185. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: FINLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: The gastrointestinal microflora is an important constituent of the gut mucosal defense barrier. We have previously shown that a human intestinal floral strain Lactobacillus GG (ATCC 53103), promotes local antigen-specific immune responses (particularly in the IgA class), prevents permeability defects, and confers controlled antigen absorption.

Objective: The aim of this study was to evaluate the clinical and immunologic effects of cow's milk elimination without (n = 14) and with (n = 13) the addition of Lactobacillus GG (5 X 10(8) colony-forming units/gm formula) in an extensively hydrolyzed whey formula in infants with atopic **eczema** and cow's milk **allergy**. The second part of the study involved 10 breast-fed infants who had atopic **eczema** and cow's milk **allergy**. In this group Lactobacillus GG was given to nursing mothers.

Methods: The severity of atopic **eczema** was assessed by clinical scoring. The concentrations of fecal alpha(1)-antitrypsin, tumor necrosis factor-alpha, and eosinophil cationic protein were determined as markers of intestinal inflammation before and after dietary intervention.

Results: The clinical score of atopic dermatitis improved significantly during the 1-month study period in infants treated with the extensively hydrolyzed whey formula fortified with Lactobacillus GG. The concentration of alpha(1)-antitrypsin decreased significantly in this group (p = 0.03) but not in the group receiving the whey formula without Lactobacillus GG (p = 0.68). In parallel, the median (lower quartile to upper quartile) concentration of fecal tumor necrosis factor-alpha decreased significantly

in this group, from 709 pg/gm (91 to 1131 pg/gm) to 34 pg/gm (19 to 103 pg/gm) ($p = 0.003$), but not in those receiving the extensively hydrolyzed whey formula only ($p = 0.38$). The concentration of fecal eosinophil cationic protein remained unaltered during therapy.

Conclusion: These results suggest that probiotic bacteria may promote endogenous barrier mechanisms in patients with atopic dermatitis and food **allergy**, and by alleviating intestinal inflammation, may act as a useful tool in the treatment of food **allergy**.

L40 ANSWER 15 OF 16 EMBASE
on STN

95339255 EMBASE Document No.: 1995339255. Oral desensitization in nickel **allergy** induces a decrease in nickel-specific T-cells. Bagot M.; Charue D.; Flechet M.-L.; Terki N.; Toma A.; Revuz J.. Department of Dermatology, Paris XII University, Hopital Henri-Mondor, 51 ave. Marechal-Lattre-de-Tassingy,94010 Creteil, France. European Journal of Dermatology 5/7 (614-618) 1995.
ISSN: 1167-1122. CODEN: EJDEE4. Pub. Country: France. Language: English. Summary Language: English.

AB Nickel (Ni) is the most frequent cause of allergic contact dermatitis, mainly in female patients. In animals, **oral tolerance** to Ni sensitization can be obtained by feeding with Ni sulfate (NiSO4). The aim of the present study was to compare the specific proliferative responses and frequencies of Ni-responding T cells from peripheral blood of patients before and after a protocol of Ni ingestion. Ten patients with chronic disseminated **eczema** and patch test-proved contact **allergy** to Ni gave informed consent for the study. All were nonpregnant female patients between the ages of 21 and 40 years (mean 35 years). They ingested 22.4 mg NiSO4 (5 mg Ni) once a week for 8 weeks. All patients experienced an exacerbation of pruritus 12 to 24 hours after ingesting the first capsules, resolving within 24 hours. Two patients had a major flare-up of their **eczema**. Eight patients completed the whole study, and presented a progressive improvement of their cutaneous lesions. In these patients, the sums of individual epicutaneous test scores were decreased after 8 weeks ($p < 0.02$). Peripheral blood lymphocytes (PBL) were isolated and stored before and after Ni ingestion. Proliferation assays were performed with 5 x 10-5 mol/l NiSO4. Stimulation indexes were decreased after 8 weeks when compared to preingestion PBL ($p < 0.02$). A limiting dilution assay was developed to quantify Ni-specific T cells from peripheral blood. The frequencies of responding T-cells were decreased after 8 weeks (1/49 061 to 1/2 517 920), when compared to preingestion PBL (1/14 547 to 1/128 682). Our results confirm that oral hyposensitization may decrease the degree of contact hypersensitivity as measured by epicutaneous tests and induce clinical improvement of cutaneous lesions. In addition, oral nickel intake can decrease Ni-specific proliferations and the numbers of Ni-responding T cells in peripheral blood. These data open a new area of investigation for the treatment of Ni **allergy**.

L40 ANSWER 16 OF 16 SCISEARCH on STN

92:687701 The Genuine Article (R) Number: JY994. DIETARY MANIPULATION AND INDUCTION OF TOLERANCE. STROBEL S (Reprint). UNIV LONDON, INST CHILD HLTH, 30 GUILFORD ST, LONDON WC1N 1EH, ENGLAND (Reprint). JOURNAL OF PEDIATRICS (NOV 1992) Vol. 121, No. 5, Part 2, Supp. S, pp. S74-S79. ISSN: 0022-3476. Pub. country: ENGLAND. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Clinical observations have suggested that the development of atopic diseases in childhood may be influenced by breast-feeding and the timing of first exposure to foreign protein, but the controversy is far from being resolved. Early weaning and introduction of foreign proteins (i.e., cow milk) have been associated with an increased prevalence of atopic symptoms in infants with a family history of atopy. Opposite results have been reported, and the effects of early protein introduction in infants

not at risk of having atopic symptoms are poorly documented. Research in rodents suggests that perinatal antigen exposure is more likely to prime the immune system than to induce tolerance. Continuous feeding beyond the critical neonatal period leads to induction of tolerance. The immunologic response is dependent on the antigen dose. Protein transfer by breast-feeding can induce tolerance, though in a dose range otherwise associated with priming. The protective effect of antigen avoidance in infancy on the development of cow milk **allergy** and also on subsequent atopic symptoms is well documented. Protective effects have been observed in infants at risk who either were breast fed or received a hydrolyzed infant formula. Several clinical studies suggest a causative role of neonatal milk exposure in the development of cow milk **allergy**. Prospective, population-based studies are required to assess the true incidence of food-allergic diseases in childhood.

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L41 0 L34 AND TICARIA

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L42 0 L34 AND UTICARIA

=> s l34 and hives
L43 1 L34 AND HIVES

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L43 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN
2002:416993 Document No. 137:351635 Cow's milk (Bos domesticus). Besler, Matthias; Eigenmann, Philippe; Schwartz, Robert H. (Hamburg, Germany). Internet Symposium on Food Allergens [online computer file], 4(1), 19-106 (English) 2002. CODEN: ISFAF8. ISSN: 1437-0573. URL: http://www.food-allergens.de/symposium-4-1/cows-milk/cows-milk-allergens.htm Publisher: Internet Symposium on Food Allergens.
AB A review. Cow's milk **allergy** (CMA) can be defined as any adverse reaction mediated by immunol. mechanisms to cow's milk proteins. CMA can be divided in IgE-mediated reactions (IgE-CMA) and non-IgE-mediated reactions (non-IgE-CMA) which may involve other Igs, immune complexes and cell-mediated reactions. Patients with non-IgE-CMA and digestive symptoms can present with the following well defined clin. pictures: milk-induced enterocolitis, milk-induced proctitis, milk-induced enteropathy, or eosinophilic allergic gastro-enteritis. CMA should be differentiated from cow' milk intolerance (CMI) reactions due to lactase deficiency or other non immune mediated causes which are not subject of the present review. Most CMA has its onset in the first year of life, and becomes apparent at the time of weaning from breastfeeding. Prevalences of DMA range from 1.6% to 2.8% in randomly selected children younger than 2 yr of age (elimination/challenge proven). **Oral tolerance** is frequently acquired in about 50 to 90% of children with CMA within the first 6 yr of life. However, severe CMA may persist into adulthood. The frequency of sensitization to cow's milk in adults has recently been estimated by RAST to be 0.7% and 1.2% in Scandinavian countries. According to the onset of symptoms after milk ingestion CMA can be classified as immediate or delayed-type. The clin. picture can vary from mild to severe, involving the skin (eczema, **hives**, angioedema), gastrointestinal tract (oral pruritis, colic, vomiting, diarrhea, constipation), respiratory tract (cough, stridor, wheezing), and cardiovascular system (anaphylactic shock). No single laboratory test is diagnostic of CMA. Clin. manifestations supported by skin tests and in vitro parameters are valuable. The diagnosis is confirmed by well-defined elimination and subsequent challenge procedures. If there is evidence of anaphylaxis, challenge should be avoided. The inadvertent ingestion of small amts. of cow's milk allergens hidden in foods can result in severe

life-threatening clin. reactions. Cow's milk allergens could be present in breast milk, infant formulas, milk and milk products like cheese and yogurt, as well as in "non-dairy" foods occurring as contaminants or unlabeled additives. The most effective treatment of CMA is allergen avoidance. Besides the optimal choice of breast milk, suitable milk substitutes in the nutrition of infants with CMA are soy hydrolyzed formulas, extensively casein and whey hydrolyzed formulas, and amino acid formulas. The exact frequency of sensitization to soy protein in children with CMA is still controversial. Soy **allergy** seems to be rare in IgE-CMA, while approx. 60% of children with milk-induced enterocolitis are sensitive to soybean. However, severe anaphylactic reactions to extensively hydrolyzed casein and partially hydrolyzed whey formulas can occur in highly sensitized infants with IgE-mediated cow's milk **allergy**. Due to the high homol. of protein composition sheep's and goat's milk are cross-reactive in approx. 80% of subjects with CMA while mare's milk is only rarely cross-reactive with cow's milk (4% in subjects with CMA). In addition, sheep's milk may cause severe IgE-mediated allergic reactions in children not affected by CMA. IgE antibodies from children allergic to cow's milk are capable of recognizing milk proteins from mammals bred in European countries (ewe, goat, buffalo). Cross-reactivity of camel's milk proteins has not bee recognized. Therefore, due to clin. important residual allergenicity in some hypoallergenic formulas and milk allergen cross-reactivity between species, clin. testing in a safe medically-supervised environment is necessary in each cow's milk sensitive infant before use. In infants and children the major cow's milk allergens are casein (CAS), β-lactoglobulin (beta-LG), and α-lactalbumin (alpha-LA). Caseins (α-, β-, κ-CAS) are the most important in children and adults. Other allergens involved in SMA are bovine serum albumin (BSA) and bovine Igs. Several IgE-binding epitopes of α-LA, β-LG, α- and β-CAS were described.
Knowledge of the immunodominant epitopes of the major allergens may be useful in identifying children who will have persistent CMA and children who aer likely to outgrow CMA. The present data collection summarizes the following topics of the major allergens may be useful in identifying children who will have persistent CMA and children who are likely to outgrow CMA. The present data collection summarizes the following topics in tabular form: prevalences of DMA, diagnostic and therapeutic features, mol. biol. and allergenic properties of cow's milk allergens, stability and hidden presence of allergens, the use of infant formulas in therapy and prevention of CMA and other atopic diseases.

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 17:25:06 ON 13 APR 2004

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L1      7779567 S TREATMENT
L2        39386 S L1 AND ALLERGY
L3           10 S L2 AND CHOLERA TOXIN B SUBUNIT
L4            6 DUP REMOVE L3 (4 DUPLICATES REMOVED)
L5            0 S L2 AND MUCOSAL ADJUDVANT
L6            0 S L2 AND E COLI ENTEROTOXIN B SUBUNIT
L7            0 S L2 AND "ETX"
L8            0 S L2 AND "ETXB"
L9            0 S L2 AND E COLI HEAT LABEL ENTEROTOXIN
L10          32 S L2 AND ENTEROTOXIN
L11          30 DUP REMOVE L10 (2 DUPLICATES REMOVED)
L12        1480 S L2 AND TOLERANCE
L13           0 S L12 AND "CTXB"
L14         411 S "CTXB"
L15           0 S L14 AND TYPE I ALLERGY
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L16            1 S L14 AND ALLERGY
L17      2899736 S COMPOSITION
L18         2213 S L17 AND ALLERGEN
L19            0 S L18 AND UNCONJUGATE
L20           53 S L18 AND TYPE I
L21            0 S L20 AND MUCOSA BINDING AGENT
L22            0 S MUCOSA BINDING AGENT
L23          104 S GM1 GANGLIOSIDE RECEPTOR
L24            0 S L23 AND BINDING AGENT
L25         4942 S ORAL TOLERANCE
L26          614 S L25 AND ALLERGY
L27            8 S L26 AND CHOLERA TOXIN B SUBUNIT
L28            4 DUP REMOVE L27 (4 DUPLICATES REMOVED)
L29           34 S L26 AND CHOLERA TOXIN
L30           18 DUP REMOVE L29 (16 DUPLICATES REMOVED)
L31            2 S L26 AND ENTEROTOXIN
L32            2 DUP REMOVE L31 (0 DUPLICATES REMOVED)
L33            0 S L26 AND COADMINISTERED
L34          361 DUP REMOVE L26 (253 DUPLICATES REMOVED)
L35           42 S L34 AND OVA
L36           42 DUP REMOVE L35 (0 DUPLICATES REMOVED)
L37           28 S L34 AND ASTHMA
L38           28 DUP REMOVE L37 (0 DUPLICATES REMOVED)
L39           16 S L34 AND ECZEMA
L40           16 DUP REMOVE L39 (0 DUPLICATES REMOVED)
L41            0 S L34 AND TICARIA
L42            0 S L34 AND UTICARIA
L43            1 S L34 AND HIVES

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L44            0 L34 AND INSECT BITE

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L45           49 L34 AND DRUG

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L46            4 L45 AND DRUG ALLERGY

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L47            4 DUP REMOVE L46 (0 DUPLICATES REMOVED)

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L47  ANSWER 1 OF 4  SCISEARCH  COPYRIGHT 2004 THOMSON ISI on STN
2003:518687   The Genuine Article (R) Number: 687DL. Oxazolone and
     diclofenac-induced popliteal lymph node assay reactions are attenuated in
     mice orally pretreated with the respective compound: potential role for
     the induction of regulatory mechanisms following enteric administration.
     Gutting B W; Bouzahzah F; Kong P L; Updyke L W; Amacher D E; Craft J
     (Reprint). Yale Univ, Sch Med, Rheumatol Sect, New Haven, CT 06520 USA
     (Reprint); Pfizer Global Res & Dev, Groton, CT 06340 USA. TOXICOLOGY AND
     APPLIED PHARMACOLOGY (1 JUN 2003) Vol. 189, No. 2, pp. 120-133. Publisher:
     ACADEMIC PRESS INC ELSEVIER SCIENCE. 525 B ST, STE 1900, SAN DIEGO, CA
     92101-4495 USA. ISSN: 0041-008X. Pub. country: USA. Language: English.
     *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB      The murine popliteal lymph node assay (PLNA) was examined as a
     preclinical assay with the potential to identify low-molecular-weight
     compounds (LMWCs) that are likely to be associated with immune-mediated
     drug hypersensitivity reactions (IDHRs) in humans. We hypothesized
     that the contact sensitizer oxazolone (OX) would cause a strong PLN
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reaction in naive mice and that the PLN reaction would be attenuated in mice orally pretreated with OX due to the induction of **oral tolerance**. In naive mice, OX induced a strong PLN reaction and caused dose-dependent increases in PLN size, weight, cellularity, percentage of CD4(+) PLN T cells, and percentage of PLN B cells, with a concomitant decrease in the percentage of CD8(+) PLN T cells. Next, the PLNA was conducted in mice gavaged three times with either OX or vehicle alone (olive oil). Mice pretreated with OX had suppressed PLN reactions following the footpad injection of OX (decrease in PLN size, weight, and cellularity), which was associated with an increase in the percentage of PLN CD8+ cells. In contrast, oral pretreatment with OX had no observable effect on the PLN reaction induced following footpad injection of the irrelevant hapten dinitrochlorobenzene (DNCB). Adoptive transfer studies were conducted to examine the mechanism of PLN hyporesponsiveness. It was found that either (1) unfractionated splenocytes or (2) purified CD8(+) splenocytes, but not (3) purified CD4(+) splenocytes isolated from mice gavaged with OX adoptively transferred PLN suppression to naive BALB/c mice. Because OX is not a pharmaceutical, we also examined the NSAID diclofenac (DF) (Voltaren). Like OX, DF caused dose-dependent increases in PLN size, weight, and cellularity in naive mice. Furthermore, like OX, the diclofenac-induced PLN reaction was attenuated in mice that had been orally pretreated three times with DF. However, splenocytes from mice orally treated with DF were not able to adoptively transfer PLN hyporesponsiveness. Collectively, these observations demonstrate that both OX and DF are potent immunostimulators in the PLNA. As importantly, these results demonstrate that the immunostimulating potential of OX and DF in the PLNA is significantly decreased in mice orally exposed to the respective **drug**, possibly due to the presence of a cellular mechanism of **oral tolerance**. For OX, the mechanism appears to involve, in part, CD8(+) T cells, whereas the mechanism(s) associated with PLN hyporesponsiveness using DF remain to be defined.

L47 ANSWER 2 OF 4 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2001:507016 Document No.: PREV200100507016. The outcome of oral challenge with alternative molecules in **drug allergy**. Bilo, M. B. [Reprint author]; Napoli, G.; Antonicelli, L. [Reprint author]; Garritani, M. S. [Reprint author]; Bonifazi, F. [Reprint author]. Allergy Unit, Department of Respiratory and Allergic Diseases, Ancona, Italy. Allergy (Copenhagen), (2001) Vol. 56, No. Supplement 68, pp. 220. print. Meeting Info.: XXth Congress of the European Academy of Allergology and Clinical Immunology. Berlin, Germany. May 09-13, 2001. CODEN: LLRGDY. ISSN: 0105-4538. Language: English.

L47 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
1998:172818 Document No. 128:212562 Immunochemical Detection and Identification of Protein Adducts of Diclofenac in the Small Intestine of Rats: Possible Role in Allergic Reactions. Ware, Joseph A.; Graf, Mary Louise M.; Martin, Brian M.; Lustberg, Lisa R.; Pohl, Lance R. (Molecular and Cellular Toxicology Section Laboratory of Molecular Immunology, National Heart Lung and Blood Institute NIH, Bethesda, MD, 20892, USA). Chemical Research in Toxicology, 11(3), 164-171 (English) 1998. CODEN: CRTOEC. ISSN: 0893-228X. Publisher: American Chemical Society.
AB Idiosyncratic adverse **drug** reactions are unpredictable, target multiple organ systems, and often become life-threatening events. Although the causes of idiosyncratic adverse **drug** reactions are not known in most cases, evidence suggests that they may be mediated through immunol. mechanisms. It is generally thought that for a **drug** to lead to an immune response, it must first become covalently bound to a carrier protein. Since most **drugs** are unreactive, it is usually a reactive metabolite that is expected to form covalent adducts. However, it is not clear why more people do not develop immune reactions against **drug**-protein adducts. One possible

explanation is that orally administered **drugs** may lead to **oral tolerance** in most individuals through mechanisms similar to that found with orally administered antigens. However, very little is known regarding the interaction of **drugs** with gut-associated lymphoid tissue of the small intestine, where **oral tolerance** can develop. As an initial step to test this hypothesis, we have investigated whether diclofenac, a commonly used nonsteroidal antiinflammatory **drug**, can lead to protein adducts in rat small intestine. Diclofenac was administered to rats by gastric gavage. Immunoblot anal. of small intestine homogenates and isolated enterocyte subcellular fractions with **drug**-specific antiserum revealed 142-, 130-, 110-, and 55-kDa protein adducts of diclofenac. The 142- and 130-kDa adducts of diclofenac were identified as aminopeptidase N (CD13) and sucrase-isomaltase, resp., by amino acid sequence analyses and by their reactions with protein-specific antibodies. The adducts were localized by immunohistochem. and found primarily in the mid-villus and villus-tip enterocytes and also in the dome overlying Peyer's patches. Similar adducts were detected immunochem. in villus-tip enterocytes of animals treated with halothane or acetaminophen. These results show that intestinal protein adducts of **drugs** can be formed in gut-associated lymphoid tissue where they may lead to the down-regulation of **drug** -induced allergic reactions in many individuals.

L47 ANSWER 4 OF 4 MEDLINE on STN
96236902. PubMed ID: 8687283. **Drug allergy**--especially on the induction of the **oral tolerance** and its specificity. Ikezawa Z. (Department of Dermatology, Yokohama City University School of Medicine, Urafune Hospital, Japan.) Arerugi = [Allergy], (1996 Apr) 45 (4) 363-70. Ref: 19. Journal code: 0241212. ISSN: 0021-4884. Pub. country: Japan. Language: Japanese.

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	641.25	641.46
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CA SUBSCRIBER PRICE	-22.18	-22.18

STN INTERNATIONAL LOGOFF AT 17:50:19 ON 13 APR 2004